RECOMBINANT DNA RESEARCH
Volume 4

Documents Relating to "NIH Guidelines for Research Involving Recombinant DNA Molecules" August - December 1978

December 1978

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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Volume 4

Documents Relating to
"NIH Guidelines for Research
Involving Recombinant DNA Molecules,"
August - December 1978

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Prepared by the
Office of the Director, NIH

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service National Institutes of Health

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PREFACE

This document is the fourth in a series constituting a "public record" of activities at the National Institutes of Health in regard to research involving recombinant DNA.

The first three volumes cover events from February 1975 through September 1978. Some highlights of that period follow:

- The Asilomar Conference, Feb. 24-25, 1975, establishes preliminary guidelines for recombinant DNA experiments
- NIH Recombinant DNA Advisory Committee (RAC) formulates proposed Guidelines, May-Dec. 1975
- NIH Director's Advisory Committee (DAC) meets to review RAC-proposed revisions, Feb. 9-10, 1976
- NIH Guidelines issued, June 23, 1976
- Federal Interagency Advisory Committee established, Oct. 1976. Proposes legislation in report of Mar. 15, 1977
- Falmouth Workshop, June 20-21, 1977, assesses risks of recombinant DNA experimentation with E. coli K-12
- RAC proposes revision of NIH Guidelines, Sept. 27, 1977
- NIH publishes final Environmental Impact Statement, Oct. 1977
- DAC meets to review RAC-proposed revisions, Dec. 15-16, 1977
- 95th Congress considers regulatory legislation, Jan. 1977-Nov. 1978
- Decision for defendant in case of Mack v. Califano, by U.S. District Court for the District of Columbia, Feb. 23, 1978; upheld by the U.S. Court of Appeals, Mar. 8, 1978
- RAC reviews Workshops (Falmouth, Ascot, Agricultural Pathogens), Apr. 27-28, 1978
- NIH issues proposed revised Guidelines, July 28, 1978
- HEW Advisory Committee on Proposed Revised Guidelines holds public hearing on NIH-proposed revision, Sept. 1978.

This fourth volume of the NIH public record contains the revised NIH Guidelines for Research Involving Recombinant DNA Molecules. The open process that led from the NIH-proposed revision to this new edition of the Guidelines, in effect since January 2, 1979, included a public hearing on September 15, 1978; an NIH-staff analysis of more than 170 letters commenting on the proposed Guidelines; an intensive review of this analysis and the letters themselves by the HEW Advisory Committee; and several meetings of the committee with groups representing the environment, industry, biological sciences, and other interests. As a result of this process, the Guidelines were modified in many respects, particularly to ensure wide notice and public participation in major decisions affecting changes.

A letter by the Director, NIH, is the first item reproduced here. It introduced several of the documents described below.

A preamble by Secretary Joseph A. Califano, Jr., follows. This is substantially the same as a press release issued by HEW on December 17, 1978, in which the Secretary announced the forthcoming publication of the Guidelines in the Federal Register.

Following the preamble is a "Decision of the Director, National Institutes of Health, To Issue Revised Guidelines for Recombinant DNA Research." This presents an analysis of all the letters and witness statements addressing the NIH-proposed revision. It explains the revision in light of the commentators suggestions, elucidating both acceptances and rejections. The appendices to the Decision include an Environmental Impact Assessment of the final Guidelines, which again affirms that activities conducted under the Guidelines pose no significant risk to the public health or the environment. Another appendix is an exchange of letters between Senators and Secretary Califano. These are concerned with the question whether to invoke extant regulatory authorities to extend NIH standards to cover all recombinant DNA research in the Nation.

Next are the revised NIH Guidelines, now in effect. The revisions relax the 1976 version in two major respects. They exempt five categories of experiments from the Guideline controls and ease restrictions on other permissible experiments. On the other hand, they require increased public participation at both the local and national levels. These requirements concern the composition and responsibilities of institutional biosafety committees (IBCs), the disclosure of public records, and an expanded role for the Recombinant DNA Advisory Committee (RAC). The Guidelines are now much more explicit in respect to implementation.

Secretary Califano requested FDA and EPA to consider applying their authorities to extend the new standards to the private sector. FDA gave public notice of intent to propose regulations that would require all recombinant DNA research leading to FDA-approved products to have been conducted according to the NIH standards. The FDA notice and the Secretary's letter to EPA are included.

Investigators using the revised Guidelines need two NIH publications--the "Administrative Practices Supplement" and the "Laboratory Safety Monograph." The former document is included in this volume. Investigators may obtain the Monograph (238 pages) from the Office of Research Safety, National Cancer Institute, Rm. 2E47C, Bldg. 13, National Institutes of Health, Bethesda, Md. 20014.

A memorandum on transition, included herein, accompanied the issuance of the revised Guidelines, setting January 2, 1979, as their effective date.

The subsequent documents in this volume are arranged in chronological order.

First is a transcript of the HEW public hearing on the proposed revised Guidelines, held in Washington, D.C., on September 15, 1978. Twenty-nine witnesses represented scientific, environmental, ethical, and governmental interests. Some wished to complete or modify their remarks in writing. All the submitted statements are reproduced here.

An HEW Committee on Recombinant DNA, which had been formed to hold the public hearing and evaluate comments, also held meetings with NIH staff and small groups representing industry, the environment, and the scientific community. In addition, the Director, NIH, held a meeting with the Federal Interagency Advisory Committee on Recombinant DNA Research, October 12, 1978, to review the proposed revised Guidelines and the expanded role of the Interagency Committee in subsequent revisions. The minutes of this ninth meeting of the committee are included. This is followed by the program of a three-day workshop symposium for the chairmen of approximately 150 IBCs, held on November 19-21, 1978, at Reston, Va., in anticipation of the augmented institutional role under the revised Guidelines.

A notable event was the awarding of the 1978 Nobel Prize in Physiology or Medicine, for contributions to the field of recombinant DNA. Congratulatory messages are reproduced.

A press release provides the names and affiliations of the newly constituted RAC, which has been expanded from 11 to 25 members to enhance its ability to deal with the legal, ethical, and other nonscientific issues surrounding recombinant DNA research.

Finally, under separate cover, are two appendices. The first contains all the letters commenting on the NIH-proposed revision, arranged chronologically and preceded by an index of names. The second comprises the summons and answer of the still-pending case of Friends of the Earth v. Califano et al., alleging the failure of the defendants to comply with the National Environmental Policy Act in issuing the NIH Guidelines.

The other volumes in this series may be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402, or viewed in some 600 public libraries through the GPO depository system. (The GPO stock number of Volume 1 is 017-040-00398-6; Volume 2, 017-040-00422-2; Volume 3, 0-726-774/1605 and, Volume 3 appendices, 0-726-773/1604.)

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

December 27, 1978

On December 15, 1978, Secretary of Health, Education, and Welfare Joseph A. Califano, Jr., approved release by the National Institutes of Health of revised NIH Guidelines for research involving recombinant DNA molecules. Enclosed are the documents as published in the Federal Register of Friday, December 22, 1978. These include: (1) a Preface by HEW Secretary Califano; (2) a Decision of the Director, NIH, on the revised Guidelines; (3) NIH Guidelines for Research Involving Recombinant DNA Molecules (revised); and (4) FDA Notice of Intent to Require Compliance with the NIH Guidelines.

As you know, the original Guidelines for such research were issued on June 23, 1976, and a revision proposed by NIH was published in the Federal Register on July 28, 1978. The Secretary then established a Departmental review committee consisting of Mr. Peter Libassi, the Department's General Counsel, as Chairperson; Dr. Fredrickson as Vice-Chairperson; Dr. Julius B. Richmond, Assistant Secretary for Health; and Dr. Henry Aaron, former Assistant Secretary for Planning and Evaluation.

The DHEW Committee held a public hearing on September 15 and reviewed all public comments on the July 28 revision. On the basis of that review, the Committee substantially revised the NIH proposal, clarifying local and national responsibilities and standards for decision-making.

Concurrent with publication of these documents in the Federal Register is the issuance of a notice of intent by the Food and Drug Administration to set requirements for compliance with the NIH Guidelines in conducting recombinant DNA research in the private sector. The Secretary has directed the FDA Commissioner and the NIH Director to prepare a plan of action for implementation of the NIH Guidelines in the private sector under FDA authorities. The Secretary has also requested the Administrator of the Environmental Protection Agency to develop requirements comparable to those of FDA.

Please let me know if you have any questions concerning these documents.

DS Fredrickson

Donald S. Fredrickson, M.D.
Director

Enclosures

federal register

FRIDAY, DECEMBER 22, 1978
PART VI

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

RECOMBINANT DNA RESEARCH

Revised Guidelines

[4110-08-M]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

RECOMBINANT DNA RESEARCH

Revised Guidelines

I am announcing today several actions affecting the conduct of recombinant DNA research in this country.

In taking these steps, I have been guided by my responsibility to allow the maximum freedom of scientific inquiry consistent with the protection of the public health and the environment and with respect for the important ethical concerns surrounding genetic research in general.

The research techniques used to produce recombined molecules of deoxyribonucleic acid, the complex chemical that codes genetic information for all living cells, hold great promise for significantly advancing our understanding of fundamental biological processes. Moreover, this research may also hold potential for the commercial production of needed biological materials and agricultural products.

From the pioneering days of this research, many of this nation's leading scientists expressed concern that the insertion of foreign genes into microorganisms could carry the potential for harm by yielding new disease-producing organisms. Although no harm has resulted from recombinant DNA research to date, there has been widespread uncertainty as to the degree of risk involved.

We must always recognize that scientific knowledge is not immutable; it is constantly changing as research generates additional information and understanding. Public policy in the field of science must therefore be flexible—to allow change as knowledge and understanding increase. The requirements that we impose must constantly be revised and updated to reflect new knowledge. Today the experience and insights that we have gained provide the basis for relaxing some of the restrictions the National Institutes of Health first imposed in 1976 on recombinant DNA research it funds.

The actions I am announcing today strive to allow the greatest freedom of scientific inquiry possible. At the same time, they provide the protections necessary to safeguard the public health and environment and also provide the opportunity for those concerned to raise any ethical issues posed by recombinant DNA research.

Specifically, I am today:

- Approving final guidelines prepared by the National Institutes of Health that significantly revise the safety requirements for conducting recombinant DNA research;
- Taking immediate steps to require that research conducted by private companies complies with the NIH guidelines, primarily through use of the regulatory authority of the Food and Drug Administration (at Appendix A);
- Requesting the Environmental Protection Agency to review its authority and to take all action it can to require compliance with the NIH guidelines by companies that carry out DNA research but whose products are not regulated by the Food and Drug Administration;
- Directing NIH to increase its research designed to determine the extent of risk associated with recombinant DNA research (at Appendix B);
- Broadening substantially the public representation on the HEW advisory committee that will assist NIH in administering the revised guidelines;
- Increasing significantly public access to information about recombinant DNA research activities and increasing public participation in the administration of the guidelines in local communities.

Revised Guidelines

The revised final guidelines that NIH has developed and that I am approving today set new directions for regulation of future recombinant DNA research. These final guidelines retain much of the guidelines that NIH published in proposed form last July. But NIH has made many revisions based on public comment and on the review conducted by a Departmental committee. The Director, NIH, has prepared a Decision Document responding to the public comments and explaining the reasons for the revision.

The final guidelines relax some of the restrictions under which recombinant DNA research has been conducted since 1976, and at the same time increase the role of the public in approving and monitoring recombinant DNA experiments.

In particular, these final guidelines relax in two major respects the guidelines that were placed in effect in 1976.

- *The revisions exempt altogether five categories of experiments from the guidelines' restrictions.* NIH has concluded that these experiments present no known health risk. Approximately one-third of research covered under the existing guidelines would be exempted under the revised standards.

The revised guidelines continue to ban all six categories of potentially hazardous research that the 1976 guidelines prohibited. They will now, however, permit the Director of NIH to grant—following public notice and comment—case-by-case exceptions to these prohibitions with appropriate safeguards.

- *The revised guidelines will ease restrictions on other permissible experiments.* Depending on the potential risk of an experiment, both the 1976 guidelines and today's revised guidelines require a researcher to comply with one of four levels of protective laboratory procedures and one of three levels of restrictions on the type of organism that may be used in the research. The revised guidelines assign almost all categories of research physical containment and/or biological containment levels at least one step lower than in the 1976 guidelines. Since the likelihood of harm now appears more remote than was once anticipated, the scientific community has now concluded that this downgrading is appropriate. The four levels of physical containment and three levels of "biological containment"—the use of weakened organisms that cannot survive outside the laboratory—set by the 1976 guidelines would remain the same.

Based on the review and public hearing conducted by a Departmental committee, the guidelines have been significantly rewritten from the July version to increase public participation at both the local and national level:

- *Twenty percent of the members of local Institutional Biosafety Committees (IBC's) must represent the general public, and have no connection to the institution.* The 1976 guidelines had no such requirements for public participation.
- *Important records must be made public.* The bulk of IBC records must be made available to the public and problems, violations, illnesses and accidents must be reported to NIH.
- *At the national level, major actions cannot be taken without advice of the Recombinant DNA Advisory Committee (RAC) with public and Federal agency comment.* Major actions include decisions to approve on a case-by-case basis experiments that are generally prohibited, to exempt additional categories of research from the guidelines, to permit the insertion of genes in new types of bacteria, and to approve changes in the guidelines themselves.

Finally, today's revised guidelines provide more explicit guidance both for local institutions and for NIH to follow in implementing the guidelines.

- Institutions must develop emergency plans covering accidental spills and personnel contamination; health surveillance programs for projects needing such safeguards; and training programs for IBC members, researchers, and other laboratory staff.
- Under the revised guidelines, the NIH Director cannot approve pro-

posed actions unless he determines that they present no significant risk to health or the environment.

Guideline Coverage

The revised guidelines apply to *all* recombinant DNA research conducted at any institution which receives NIH funds for recombinant DNA research. At these institutions, even research conducted without NIH support must comply with the guidelines. Other research agencies of the Federal government have assured us that they will require compliance with the NIH guidelines for all recombinant DNA research that they conduct or support.

We are also taking action to assure that the guidelines apply, to the greatest extent possible, to research conducted in the private sector.

● At my direction, the Food and Drug Administration is today announcing its intent to propose than any recombinant DNA research submitted to satisfy FDA's regulatory requirements must have been conducted in compliance with the NIH guidelines.

● I have also written to Douglas Costle, the Administrator of the Environmental Protection Agency (EPA) and asked him to review EPA's regulatory authority to determine whether EPA can regulate recombinant DNA research conducted privately that is not submitted to the FDA. I have asked him to take all action he can.

If both FDA and EPA act to regulate privately conducted recombinant DNA research, virtually all recombinant DNA research in this country would be brought under the requirements of the revised guidelines.

Broadened Committee Membership

I will announce shortly the names of 14 new members of HEW's recombinant DNA Advisory Committee. In addition to scientists who are experts in molecular biology and other disciplines, the Committee will be expanded to include persons knowledgeable in a wide variety of fields such as law, public policy, ethics, the environment and public health. The Committee will serve as the principal advisory body to the Director of NIH and to the Secretary of HEW on recombinant DNA policy.

Increased Risk Assessment Research

While our knowledge about the risks of recombinant DNA has increased dramatically, much remains unknown. The scientific community must continue to assess the extent of the risks posed by recombinant DNA research. I am therefore directing the Assistant Secretary for Health and the Director of the National Institutes of Health to formulate a plan for carrying out a balanced program of additional risk assessment experiments. In my view, the more risk assessment experiments NIH conducts or supports, the better we can judge whether the guidelines—and actions taken under them—afford appropriate protection for health and the environment.

Today's action represents the culmination of a long and thorough process that has sought at each step to balance the important concerns involved in recombinant DNA research. The National Institutes of Health in 1976 published guidelines to govern research which it funds.

The 1976 guidelines:

● Prohibited six categories of recombinant DNA experiments which experts felt posed significant hazards.

● Defined degrees of physical and biological containment necessary to prevent recombinant DNA organisms from escaping into the environment and surviving.

● Described permissible categories of recombinant DNA research and assigned levels of physical and biological containment for each.

● Described specific roles and responsibilities for principal investigators, research institutions, institutional biohazard committees, and the NIH.

Since issuance of the 1976 guidelines, recombinant DNA techniques have become much more widely used in research, and more has been learned about the limits of potential risks in using this technology.

In light of this new knowledge, the Director, NIH, on July 28, 1978 proposed substantial modification and relaxation of the guidelines. At that time, I named a Departmental review committee consisting of Peter Libassi, the Department's General Counsel, as Chairperson; Dr. Donald Fredrickson, the Director of NIH, as Vice Chairperson; Dr. Julius Richmond, Assistant Secretary for Health; and Dr. Henry Aaron, then Assistant Secretary for Planning and Evaluation. I asked the Committee to examine the proposed guidelines and to hold a public hearing on the guidelines.

In reviewing the guidelines, the committee solicited and heard comments from representatives of environmental groups, unions, pharmaceutical companies, institutional biosafety committees and Congressional staff members. The committee reviewed more than 170 letters from the public commenting on the revisions. The committee planed a vital role in the process which led to the revised guidelines and unanimously recommended that the revised guidelines be approved.

These revised guidelines provide for a flexible, open system that can accommodate new scientific information that may warrant change, either to relax or to increase safety requirements.

I applaud all who have labored to develop these guidelines: The scientific community, the public, and workers at the Federal, State and local levels. This research holds promise for adding to our understanding about basic biological processes. These guidelines should permit that promise to be realized without presenting any significant risk to public health or the environment.

Dated: December 15, 1978.

Joseph A. Califano, Jr.,
Secretary.

Appendix A

The Secretary of Health,
Education, and Welfare,
Washington, D.C. 20201.

December 15, 1978.

MEMORANDUM TO: Commissioner of Food and Drugs, Director, National Institutes of Health.

THROUGH: Assistant Secretary for Health.

SUBJECT: FDA Requirements for Compliance with the NIH Guidelines for Recombinant DNA Research.

With my approval and that of the Assistant Secretary for Health, the Director of the National Institutes of Health is issuing today revised Guidelines for Recombinant DNA Research.

These Guidelines set down requirements for all recombinant DNA research either conducted by NIH or conducted by institutions receiving NIH funds for recombinant DNA research. Other Federal agencies funding recombinant DNA research have agreed to require recipients of their funds to comply with these Guidelines as well.

To the maximum extent possible, we should extend the coverage of the NIH Guidelines to recombinant DNA research carried out in the private sector, with appropriate protection for proprietary and patent rights.

As we discussed, the pharmaceutical industry does most of the recombinant DNA research that is carried out privately in this country. Accordingly, the Food and Drug Administration is issuing today a Notice of Intent to propose regulations. These proposed regulations would require that all recombinant DNA research submitted to the FDA to satisfy the FDA's regulatory requirements be carried out in compliance with the Guidelines. This requirement should bring under the Guidelines the vast majority of recombinant DNA research conducted in this country by the private sector. If FDA does adopt such regulations, there must be close cooperation between NIH and FDA in implementing them. With the Commissioner of Food and Drug taking the lead, you should prepare a plan of action on the steps necessary to apply the Guidelines to the private sector.

Please submit a memorandum describing your proposed plan of action at the time you submit proposed regulations.

Joseph A. Califano, Jr.

APPENDIX B

THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE,
Washington, D.C. 20201.

DECEMBER 15, 1978.

MEMORANDUM TO: Assistant Secretary for Health, Director, National Institutes, National Institutes of Health.

SUBJECT: Assessing the Risk of Recombinant DNA Research.

With the issuance today of revised Guidelines for recombinant DNA research, the responsibility of the National Institutes of Health to conduct and support experiments designed to determine the risks of recombinant DNA research becomes even more important than it has been in the past. The revised Guidelines now require a finding by the Director of NIH that each proposed action under the Guidelines "presents no significant risk to health or the environment." It is critical that these judgments, to the maximum extent possible, be based on the firm foundation of documented research that is subject to peer review.

Experience and knowledge gained from the broad range of recombinant DNA research already underway will provide much information for assessing risks. But in many areas special research and careful attention will be needed. To discharge our responsibility to assess risk before certain research is conducted on a wide-spread basis, NIH should formulate a plan for carrying out a balanced program of more such risk-assessment experiments either at NIH directly or under NIH-supported grants or contracts. In my view, the more risk assessment experiments NIH carries out, the better we will be able to judge whether the Guidelines—and actions taken under them—afford appropriate protection for health and the environment.

Your overall plan to conduct risk assessment experiments should be published for public comment and presented for review to the Recombinant DNA Advisory Committee annually. The first such plan should be ready for publication and submission to the Advisory Committee by March 30, 1979.

JOSEPH A. CALIFANO, Jr.

NOTICE OF RELEASE OF REVISED NIH GUIDELINES FOR RECOMBINANT DNA RESEARCH

Today, the Director, National Institutes of Health, with the approval of the Assistant Secretary for Health and the Secretary of Health, Education, and Welfare, is authorizing the release of revised *NIH Guidelines for Research Involving Recombinant DNA Molecules*. The *Guidelines* and a *Decision* of the NIH Director to issue the revised guidelines are published below.

Dated: December 15, 1978.

DONALD S. FREDRICKSON,
Director,
National Institutes of Health.

DECISION OF THE DIRECTOR, NATIONAL INSTITUTES OF HEALTH, TO ISSUE REVISED GUIDELINES FOR RECOMBINANT DNA RESEARCH

DECEMBER 1978.

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I. SCOPE OF THE GUIDELINES

A number of commentators at the September 15 hearing and correspondents addressed issues concerning the scope of the Guidelines. Views were expressed for an against exempting experiments from the Guidelines even though some argued that the risk was minimal or nonexistent. Specific issues that were raised are discussed below.

GENERAL APPLICABILITY

Several commentators spoke to the scope of the applicability of the Guidelines. Some questioned the right of NIH to apply the Guidelines to investigations not supported by NIH at an institution that receives some NIH funding for recombinant DNA research. Others, however, urged that the scope be broadened to include all institutions receiving NIH or, indeed, DHEW funding for whatever purpose.

I addressed these concerns in my Decision accompanying the proposed revision published in the FEDERAL REGISTER on July 28, 1978. I noted that partial adherence to the Guidelines within an institution would defeat the purpose of extending maximal protection to the community. Thus, it would be inconsistent for NIH to provide funds for recombinant DNA activities to an institution that did not meet the standards of the Guidelines in all of its recombinant DNA research, regardless of the source of funding. This principle is sound and NIH has the authority to apply it.

Some commentators took exception to the statement in the section on General Applicability that once certain research is approved at the local level, it may proceed. Several correspondents pointed out that the language conveys the sense that all recombinant DNA research can proceed solely on the basis of local approval. This is not the case and this section does not, in fact, deal appropriately with the matter. Accordingly, the topic has been deleted from the Applicability section and dealt with extensively in part IV of the Guidelines and in the Administrative Practices Supplement.

Another commentator urged that the requirements of the Guidelines be extended to NIH-supported research in foreign countries. The proposed revised Guidelines (PRG) state that the Guidelines are applicable, but if the host country has rules for the conduct of recombinant DNA projects, then a certificate of compliance with those rules may be submitted to NIH in lieu of compliance with the NIH Guidelines, so long as the safety practices of the two are reasonably consistent. Of course, in countries with no guidelines, the NIH Guidelines must apply to NIH-supported research.

PROHIBITIONS AND EXEMPTIONS—GENERAL COMMENTS

There were a large number of comments on prohibitions, exceptions to prohibitions, and exemptions from the Guidelines. There was some confusion on the difference between exceptions and exemptions. Experiments excepted from the prohibitions are assigned appropriate containment levels and thus must be conducted in compliance with the Guidelines. For experiments under the exemptions (and not affected by prohibitions), the Guidelines do not apply at all.

Several of the commentators spoke to one or more of the criteria used for exempting experiments from the Guidelines. Some said that the criterion for granting exemptions should be safety and not whether DNA exchange occurs in nature. This issue is discussed in the Environmental Impact Assessment accompanying the revised Guidelines in the FEDERAL REGISTER of July 28, 1978.

It was noted there that, according to some commentators, safety rather than "novelty" should be the criterion for exclusion. That is, any recombinant molecule that poses a potential threat to the public health or the environment should be covered by the Guidelines regardless of whether the molecule is a novel one. An opposing view, expressed by other commentators, was that a proper criterion should be whether the potential hazard of the recombinant molecule would differ significantly from the biohazard posed by a molecule already found in nature or from a biohazard that can be successfully handled by conventional methods. It proved impossible to reconcile these differences of opinion in the definition itself, and

so the Exemptions sections was developed.

In my view, the criteria given in the exemptions and prohibitions sections of the PRG defining recombinations similar to natural events are both conservative and reasonable. It should be noted that the wording of prohibition I-D-5, "that are not known to acquire it naturally," is identical to that of the original 1976 Guidelines.

PROHIBITIONS—SPECIFIC COMMENTS

Several commentators requested clarification of prohibition I-D-2 concerning the deliberate formation of potent toxins. Was it intended to cover only toxins for vertebrates or those for all species? A commentator noted that fungi produce antibiotics that are potent toxins for bacteria. It is not the intent of this prohibition to cover such toxins but only potent toxins for vertebrates. Accordingly, new language makes it clear that "potent toxins" refers specifically to vertebrates.

A number of commentators form the agricultural community urged that mechanisms be set in place for waiver of prohibition I-D-4, which bans deliberate release into the environment of any organism containing recombinant DNA. Recognizing the need expressed by these commentators for more definitive standards for allowing exceptions, I will refer the matter to the Recombinant Advisory Committee (RAC) for its consideration. Indeed, in response to several suggestions from commentators, the RAC will be asked to address conditions under which exceptions to various prohibited categories of experiments may be granted.

Another commentator urged that for waiver of the prohibition on deliberate release into the environment, the Guidelines explicitly require compliance with the National Environmental Policy Act (NEPA) and any additional safeguards to be stipulated by EPA. Others urged that full Environmental Impact Statements be filed on most exceptions to the prohibitions. As I noted in my Decision accompanying the PRG on July 28, 1978, all waiver decisions will include a careful consideration of the potential environmental impact. Some decisions may be accompanied by a formal assessment or statement—a determination, however, that can only be made on a case-by-case basis. In the new procedures for the Federal agencies under the Guidelines, all agencies represented on the Federal Interagency Committee, including EPA and OSHA, will have nonvoting members on the RAC, and will thus have opportunity to participate in all the RAC's deliberations. In addition, the Federal Interagency Committee may be convened to discuss issues its members believe are important prior to the granting of any waiver. Exceptions to prohibitions also fall under the procedure described in Section IV-E-1-b-(1) of the Guidelines that involves at least 30 days of public comment.

The standard for exceptions to prohibitions in the Guidelines was a source of much comment. Some commentators believe that the standard should be "no significant risk and a clear social benefit to be realized." Others urged that exception to the prohibitions be justified only to permit special risk-assessment experiments. I believe that Section IV-E-1-b sets the appropriate standard at this time. This is particularly so in light of the new procedural protections described in part IV requiring public and Federal agency participation in such decisions.

There were a number of comments from the private sector concerning the prohibition on large-scale experiments (I-D-6). They noted that the necessity for conducting scale-up experiments (greater than 10-liter volumes) is imminent, and that, in their view, such experiments present no unusual hazards. I recognize the need for conducting experiments with more than 10 liters of culture and the extensive experience of industry in dealing with larger volumes. The criteria set forth in the Guidelines make the prohibition inapplicable when the recombinant DNAs are rigorously characterized and free of harmful DNA sequences. An exception to the prohibition may also be granted [see Guidelines, Section IV-E-1-b-(1)-(e)] and the RAC will begin to consider specific standards for exceptions.

EXEMPTIONS—SPECIFIC COMMENTS

In the PRG all of the prohibitions overrode the exemptions. There were suggestions that certain prohibitions not apply to the exemptions. It was recommended, for example, that the prohibitions relating to the deliberate release of recombinants into the environment and the deliberate transfer of drug resistance not apply to exempt experiments. In my view these prohibitions must continue to apply for the present.

It was also argued that the prohibition on large-scale experiments should not apply to exempt experiments. This prohibition, indeed, is different from the other five, as is explicitly noted in the 1976 Guidelines. In the PRG the language was tightened: "recombinant DNAs known to make harmful products" was changed to "unless the recombinant DNAs are rigorously characterized and are shown to be free of harmful genes." For experiments in the exempt category that call for more than 10 liters of culture, it seems unnecessary to have the recombinant DNAs meet these criteria. Therefore, a fixed prohibition, unduly restrictive in these cases, no longer applies, and experiments which meet the criteria of the exemptions may be conducted in volumes of over 10 liters. The first five prohibitions continue to apply to all experiments and override the exemptions.

A correspondent stated that the inclusion of specific exemptions in the Guidelines is premature. It was recommended that exemptions be granted instead on a case-by-case basis after risk-assessment, NEPA compliance, public participation, and a finding based on experimental data that the exemption presents no significant risk to health or the environment. In my view the five classes of exemption listed in the PRG, as discussed in the accompanying Decision Document and Environmental Impact Assessment, are warranted. It is a view shared by the RAC and many commentators throughout this long period of proposed Guideline revision. All of the participants and observers concerned with the Guidelines will benefit from disengagement of the least potentially hazardous use of recombinant DNA techniques, so that attention may be focused on the areas still encompassed by the Guidelines.

A witness at the September 15 hearing objected to exemption of experiments involving naked DNA, maintaining that the Rowe-Martin experiment showed that the ingestion of naked polyoma DNA by mice resulted in infection. This is incorrect. In that experiment the DNA caused infection in mice only when injected, and then with much reduced ability as compared with the whole virus. It is a common experience that naked DNA molecules are fragile and difficult to retain intact in the laboratory. Ingested DNA would be destroyed in the alimentary tract by stomach acid and the various enzymes that degrade DNA. The one route whereby naked DNA molecules might be hazardous is accidental injection, as into a laboratory worker, The same could be said for many of the chemicals used in experiments. For this reason, the use of hypodermic needles in laboratory procedures is avoided whenever possible. Their use is specifically discouraged in the section of the Guidelines on Containment. Further, Footnote 5 has now been expanded to recommend inactivation of DNA before disposal, and specifically refers to the, Laboratory Safety Monograph as a source of advice on acceptable methods.

A commentator on behalf of the RAC's Working Group on Prokaryotic Host-Vectors Other than *E. Coli* K-12 proposed modification of Exemption I-E-3. He provided the following justification: "Addition of the proposed clause ['or which have been trans-

ferred to another host by known physiologic means"] will exempt the following types of experiments:

"An *E. coli* strain is constructed in which a chromosomal gene of *E. coli* has been enzymatically joined to plasmid DNA; this plasmid is then transferred by conjugation into another bacterial host that is not on the Director's List of bacteria that exchange with *E. Coli*.

"It seems logical that this experiment should be exempt, because it involves natural genetic exchange between two organisms both of which are exempt. The *E. Coli* donor is exempt because it represents a gene combination that could easily arise by natural means. As the transfer can also occur naturally, the same statement applies also to the second host carrying the plasmid.

"If unidirectional plasmid transfer had been accepted as an adequate criterion for inclusion on the Director's List, the strain would be automatically exempt. The reason for not accepting this criterion was that some doubts had been expressed as to whether unidirectional plasmid transfer automatically implied bidirectional transfer of chromosomal genes. However, in the present case, the ability to construct the desired recombinant is *de facto* evidence that it could arise by natural means.

"A specific proposal was submitted to RAC • • • to splice an *E. Coli* suppressor into an *E. Coli* transposon, then move the resulting combination into Myxococcus by P1 transduction. This strategy will allow the isolation of suppressible mutants of myxococcus and its phages, which will greatly expedite genetic studies of development and motility in that organism."

The change as proposed by the commentator is warranted in my view, and has been made, with minor rewording for clarity.

There were many comments concerning the list of exchangers in Appendix A to be exempt from the Guidelines under exemption I-E-4.

Many commentators urged more explicit standards for inclusion on the list. As discussed in detail in the section of this document dealing with Appendix A, the criteria for inclusion on the list have been tightened and made more explicit, reducing the list considerably and thus exempting fewer experiments from the Guidelines.

II. Containment

The object of the containment provisions of the proposed revised Guidelines is to ensure that experimental DNA recombination will have no ill effects on the researchers, the general public, or the environment. Public comments on part II of the Guidelines and on the Laboratory Safety Monograph were generally supportive. However, a number of pertinent issues relating to physical and biological containment were raised in correspondence and at the public hearing held on September 15, 1978. They deserve consideration and are addressed below.

PHYSICAL CONTAINMENT

Effectiveness of Physical Containment

One commentator observed that laboratories cannot provide foolproof containment of dangerous organisms and that a biohazard outbreak can rapidly spread to virtually any neighborhood on earth. He cited the recent laboratory accident in England attributed to the escape of a smallpox virus through a faulty filter. NIH agrees that when known hazardous agents are dealt with, the risk of a laboratory-acquired infection cannot be totally eliminated. I believe, however, that adherence to the Guidelines provides ample protection for laboratory personnel, the public, and the environment. Even if an organism should escape from the laboratory, the mutational changes underlying "biological containment" would greatly decrease the probability that it would survive in the environment. The recent incident in England involves an extraordinarily hardy, resistant, and virulent organism to which man is very susceptible—one that is hardly comparable to weakened strains of *E. coli* generally used in recombinant DNA research or to the new host-vector (HV) systems now under consideration.

Laboratory Practices

A correspondent noted that persons on antibiotics or immunosuppressive drugs, or those with open lacerations or chronic digestive abnormalities, are not prohibited from entering the laboratory under any of the physical containment levels. In response, it should be pointed out that the *Laboratory Safety Monograph* (LSM), page 204, provides that "laboratory workers who are undergoing treatment with steroids, immunosuppressive drugs or antibiotics, or are suffering from colitis, ileitis, active chronic diarrhea, or other gastrointestinal disorders, should have a medical evaluation to determine whether they should be engaged in research with potentially hazardous organisms during the time of their illness." Reference to this now appears in Section IV-D-1-h, which also mandates that the institution shall provide health surveillance of laboratory personnel.

Several commentators noted that absence of specific guidance for the rodent and insect control programs required in Section II-B-1-a-(9), II-B-2-a-(12), II-B-3-a-(12), II-B-4-a-(16). The large variety of situations and animal involved makes precise specifications impractical. It is the intent of the Guidelines, however, that adequate attention be paid to this problem, and further guidance will be provided in the next edition of the LSM.

Emergency Procedures

One commentator urged that the Guidelines include specifications for cleanup procedures to be followed in the event of a spill or accidental release of organisms into the environment. A witness recommends that for prompt and adequate response to emergencies, a team of experts from NIH and CDC be formed, and that their names and telephone numbers be published for easy access. Emergency procedures are currently detailed in the LSM, pp. 194-195. These will be expanded in the next edition of the monograph to provide for an NIH-CDC emergency consultation and response program to assist institutions in managing serious accidents. Twenty-four-hour telephone coverage will afford an immediate reponse capability.

One correspondent recommended that all bacteria used in recombinant DNA experiments be tagged so that their spread, in the event of an accident, could be detected in the environment. A general requirement to this effect is not now practicable. It should be noted, however, that in many cases bacteria are tagged to permit identification.

A correspondent raised the prospect that P2 and P3 containment facilities could be compromised by an earthquake. Most institutions have emergency plans for dealing with natural disasters. Selected references are cited in the LSM. If necessary, NIH and CDC are available to provide direct assistance in the management of specific emergency situations. Moreover, institutions in areas subject to natural disasters such as earthquake must generally conform to building code requirements that are designed to minimize the effects of such disasters.

Issues Related to Specific Containment Levels

A number of additional comments were received from public commentators relating to the proposed actions at specific levels of physical containment.

One correspondent said that the new P1 and P2 containment conditions are not significantly different, and that the difference between P1 and P2 should be approximately the same as that between HV1 and HV2. He objected strongly to the escalation of the P1 and P2 containment rules.

NIH believes that the differences between the two levels of containment are significant. For example, P2 requires use of biological safety cabinets to contain aerosol-producing equipment, use of the universal biohazard

sign, and use of gowns, coats, and uniforms. It limits entry into a laboratory to those who have been specifically informed advised of the nature of the research being conducted.

In response to a witness who averred that P1 actually represents *no* containment, it can be noted that P1 is the equivalent of the physical-containment level used in medical microbiological and hospital diagnostic laboratories throughout the world for handling infectious organisms. Indeed, it was suggested that a need exists for an even lower level of physical containment than P1 (for organisms considered of minimal risk). I do not believe it prudent, however, to permit a lower level of containment for experiments covered by the Guidelines.

In the *Decision of the Director* published with the NIH-proposed revised Guidelines on July 28, 1978, I indicated that mouth-pipetting would no longer be permitted in P1 containment. Since it is already prohibited in P2 through P4 containment, this would ban the use of mouth-pipetting for any experiment covered by the Guidelines. One commentor feels that mouth-pipetting should not be prohibited under P2 conditions and should definitely be allowed under P1 containment because of its superior efficiency. The banning of mouth-pipetting at the P1 level, however is in accord with the advice of safety experts; the present availability of excellent mechanical devices for pipetting makes the alternative, in my opinion, a practicable one.

A correspondent suggested that use of biohazard signs at the P2 level of containment should be discontinued: "They should be reserved for demonstrated biological hazards. There is a real danger that overuse of these signs in cases where workers know they do not apply will lead to the ignoring of *all* biohazard signs." While I recognize the concern expressed, I feel it prudent to require the universal sign at the P2 level when recombinant DNA materials are being handled.

For the P3 level of containment, one commentator suggested that an autoclave be within the controlled laboratory area, if not the laboratory itself, rather than merely in the same building. Another commentator makes a similar point for the P2 level. This issue was raised in comments on the revision of the Guidelines proposed by the Recombinant DNA Advisory Committee (PRG-RAC, FEDERAL REGISTER, September 27, 1977). As stated in my *Decision* (FEDERAL REGISTER, July 28, 1978), "* * * an absolute requirement that the autoclave must be within the controlled area is not considered appropriate, since contaminated material can be safely transported. Such a requirement would exclude the use of autoclaves in waste-staging areas that have been conveniently sited to support an entire facility."

A commentor questions for entrance of children into P3 facilities. After considering this issue, I have decided to (1) retain the stipulation that persons under 18 years of age shall not enter a P4 facility, (2) raise the age limit for entry to P3 laboratories from 12 to 16 years of age, and (3) eliminate the age stipulation for P2 laboratories.

A recommendation that the use of a separate centrifuge room or cubicle be provided in a P3 facility to contain spills occasioned by rotor failure has not been accepted. All rooms in the P3 facility must be capable of being sealed to facilitate space decontamination. Modern centrifuges do not present the potential hazard associated with earlier models. Rotor design, operation requirements, the design integrity of the centrifuge well, and the availability of sealed centrifuge cups adequately control the aerosol hazard associated with centrifuging.

Other concerns relating to the P3 level of physical containment have been considered:

- Section II-B-3-c-(7), dealing with ventilation, has been completely rewritten to clarify the intent to permit recirculation of HEPA-filtered exhaust air.
- Section II-B-3-c-(5), which requires that laboratory doors be self-closing, has been deleted. As a correspondent observes, the Guidelines should be worded in such a way as to make facility design compatible with Section II-B-3-a-(1) requiring laboratory doors to be closed while experiments are in progress has been retained.
- A recommendation that the Guidelines be revised to require that booties be worn at all times within the P3 laboratories has not been accepted.

For the P4 level of physical containment, one correspondent would have the Guidelines specifically require the use of gloves. In response, it can be noted that most P4 experiments use Class III cabinets, which are fitted with attached arm-length rubber gloves. As shown in Table II of the PRG-NIH, however, one can work in open-faced biological safety cabinets with augmented biological containment. In this case, the requirement for gloves has now been explicitly set forth by addition of text to Table II.

In response to commentors' suggestions and NIH review, other changes have been made in the Guidelines. For example:

- Sections II-B-1-a-(5), II-B-2-a-(5), and II-B-3-a-(5) have been changed to indicate that eating, drinking, smoking, and storage of foods are not permitted in the "laboratory area in which recombinant DNA materials are handled."
- Sections II-B-2-a-(10) and II-B-3-a-(11) have been changed to mandate the posting of the universal biohazard sign on freezers and refrigerators "or other units" used to store organisms containing recombinant DNA molecules. In addition, the requirement for identifying storage units within the P4 facility with the universal biohazard sign has been included in Section II-B4-a-(15).
- Additional language to clarify the use of the terms "sterilized" and "decontaminated" has been added to Sections II-B-1-a-(3), II-B-2-a-(3), II-B-3-a-(3), II-B-3-a-(8), II-B-4-a-(9), and II-B-4-a-(10).
- The requirement that the laboratory be kept neat and clean has been added to P1; it was already present at P2, P3, and P4.
- A new Section II-B-4-(18) has been added concerning vacuum outlets in the P4 facility.

SHIPMENT

New language to clarify the intent of Section II-C relating to shipment has been suggested by the Department of Transportation. This language has been incorporated (with minor modifications) into the Guidelines. The suggestion of one correspondent that certain clones be exempt from these requirements has not been accepted.

BIOLOGICAL CONTAINMENT

Certification of Host-Vector Systems

Most comments on the biological containment provisions of the proposed revised Guidelines related to development, review, and approval of host-vector (HV) systems other than *E. coli* K-12. In particular, commentators from the scientific community continue to urge development of such alternate systems. Thus, one correspondent wrote, "The anticipated potential of recombinant DNA in agriculture will be difficult, if not impossible, to realize with *E. coli* K-12 host-vector systems. Therefore, it is imperative that attention be given to the development and approval of alternate HV1 systems that may be useful in genetic engineering of plants and invertebrates." Another correspondent wrote, "While many of the regulations do not add to the safety of what are basically safe experiments, they do serve to inhibit the development of new and versatile vector systems * * *. The redundant safety testing program is too onerous, time-consuming, and in our opinion, not scientifically justified."

While I agree that research based on other host-vector systems must proceed, I believe that certification of these systems should be approached conservatively. The new systems raise

ecological and biological issues that must be carefully and thoughtfully addressed. As one correspondent cautions, "We must be very careful when, bolstered by our confidence in *E. coli* K-12 systems, we try to extrapolate to *B. subtilis*, yeast, etc." Two Working Groups of the RAC have recently met to consider alternate systems and to develop more precise and objective criteria for certification.* Many problems, however, persist for setting general standards that could be applied to all organisms. I believe that the process of review and approval described in the Guidelines will allow for full and deliberate examination on a case-by-case basis of putative HV systems and of pertinent ecological and biological issues. This process will, of course, comply fully with NEPA.

In response to one correspondent's suggestion, text has been added to Section II-D-2-a further clarifying the roles of the NIH Director and ORDA in the process of certification.

Data Required for Certification

One correspondent suggested an expansion of Section II-D-2-b-(1), relating to data to be submitted for certification of HV1 systems other than *E. coli* K-12. Specifically, he would require a thorough discussion of the physiological properties of the organism, particularly those related to its reproduction and survival and the mechanisms by which it exchanges genetic information—not simply the range of organisms with which it exchanges. I believe these characteristics to be especially crucial in approval of new systems; accordingly, Section II-D-2-b-(1) has been amended to incorporate this suggestion.

EK1 Systems

One correspondent noted that most host components of EK1 systems used in recombinant DNA research have mutations in addition to those acquired during K-12's laboratory evolution that confer special nutritional requirements, cause recombinants to be defective, or otherwise diminish survival or reduce the likelihood for transmission of recombinant DNA. It has been suggested that use of such mutations should be encouraged. In my view, much of the value of the EK1 host is its flexibility, and it does not seem necessary to explicitly recommend certain strains of *E. coli* K-12 as EK1 strains. The investigator will generally choose the more readily transformable *E. coli* K-12 strains, and many of the characteristics that enhance transformability decrease survival. In addition, by suggesting the use of certain mutations, we may shut off research on others which might prove even more useful and safe.

FLEXIBILITY IN CHOOSING PHYSICAL AND BIOLOGICAL CONTAINMENT LEVELS

One witness and one correspondent questioned the rationale for allowing alternate levels of physical and biological containment. The concept of "flexibility" is discussed at some length in the *Decision* document, FEDERAL REGISTER, July 28, 1978, pp. 33052-33053, and in the accompanying *Environmental Impact Assessment*, p. 33113. Moreover, the flexibility allowed in alternate P and HV levels is carefully explained in the text of the Guidelines, and the investigator must follow the explicit requirements set forth in part III of the Guidelines and Tables I and II.

III. CONTAINMENT GUIDELINES FOR COVERED EXPERIMENTS

GENERAL CONSIDERATIONS

Many of the commentators supported the levels of containment recommended for covered experiments. They concurred with the scientific arguments presented in the Decision document and Environment Impact Assessment (issued July 28, 1978) as a rationale for lowering containment levels. Some cited the reports of the Falmouth and Ascot risk-assessment meetings as confirmatory evidence, and reiterated that *E. coli* K-12 cannot be converted into an epidemic pathogen even by the introduction of additional genes from known pathogenic strains.

Many commented favorably on specific sections of the Guidelines, such as the lowered containment levels for viral DNA. Others supported the proposed containment levels for the cloning of primate DNA. One further stated that relaxation would permit major studies to be made in locating and mapping human genes. Another noted that the proposed revisions would permit the conduct of research with plants and plant-associated microorganisms and endorsed the changes based on the Workshop on Risk Assessment of Agricultural Pathogens.

A number of commentators, while generally supportive of the changes proposed, believed the Guidelines to be still too restrictive. Some urged that they either be dispensed with entirely or, in the opinion of one commentator, be replaced with the following sentence: "It would seem prudent to conduct work with organisms containing recombinant DNA under laboratory conditions appropriate to the degree of pathogenicity of the donor organisms."

I appreciate the thoughtfulness and care that have gone into the many letters. I also acknowledge a belief that the proposed revised Guidelines represent a conservative lowering of containment based on data and analysis discussed in detail in the Decision document and Environmental Impact Assessment of July 28, 1978.

On the other hand, there were commentators and witnesses who believed the lowering of containment levels in the proposed revised Guidelines was not justified. While there was a difference of emphasis in many of the comments, there appeared to be several major concerns. I shall consider each of these in turn.

● Commentators state that "much of the evidence [that NIH cites as a basis for lowering containmant] has never been published or is available only in summary form." Also that "A great deal of weight has been placed on semi-authorized reports of discussions held at closed scientific meetings, attended by a small number of selected participants." They express concern that such action by NIH has prevented the wider scientific community from critical appraisal of the data. Various of these commentators state that the results of the Falmouth conference were published only two months before the proposed revision of the Guidelines was issued, that the proceedings of the Ascot conference have not been issued, and that the results of the Rowe-Martin risk-assessment experiments have not yet been published.

The extensive proceedings of the Falmouth meeting, held in June 1977, were published in the *Journal of Infectious Diseases* in May 1978. Publication in journal form usually involves a considerable delay, even after the edited manuscript, in this case constructed of transcripts of papers and discussions edited by participants, has been completed. The moderator of the Falmouth meeting, Dr. Sherwood Gorbach, Professor of Medicine and Microbiology, Tufts University School of Medicine, summarized the outcome of the meeting in a letter to me on July 17, 1977. (This letter was published as Appendix M to the October 1977 Environmental Impact Statement, and was also published along with letters from other participants in the *Recombinant DNA Technical Bulletin*, Volume 1, No. 1, Fall 1977.)

The report of the Ascot meeting was published as Appendix E to the Environmental Impact Assessment (EIA) in the FEDERAL REGISTER on July 28, 1978, pp. 33159-33167, and previously in the FEDERAL REGISTER on March 31, 1978, pp. 13748-13755: Its introduction says, "A draft of this report was sent to the members for comment and revi-

*The Working Group on Prokaryotic Host-Vectors Other Than *E. Coli* met on September 12, 1978; and the Working Group on Lower Eukaryote Host-Vector Systems met on September 16, 1978.

sion, and this final version is based on the replies of all the participants."

The report of the Virus Working Group, which considered the Ascot Report, was published as Appendix F to the EIA in the FEDERAL REGISTER July 28, 1978, pp. 33167-33174.

The 36 participants at the Falmouth meeting are listed in the report of the meeting (*Journal of Infectious Diseases*, Vol. 137, pp. 613-614, May 1978). Most of the participants were invited by the organizing (steering) committee for the meeting, and the members of that committee are listed on these pages. In addition to invited participants, others arrived uninvited and participated.

The participants and the reasons for holding the Ascot meeting are discussed in my Decision document (FEDERAL REGISTER, July 28, 1978, p. 33060) and in the EIA, p. 33159.

The participants in the Virus Working Group, which met on April 6-7, 1978, to review the report of the U.S.-EMBO Workshop, are described in the EIA. (FEDERAL REGISTER, July 28, 1978, p. 33167). This meeting was announced in advance in the FEDERAL REGISTER on March 17, 1978; it was entirely open and was attended by others than the participants.

The results of the Falmouth, Ascot, and Virus Working Group meetings were discussed at a number of meetings of the Recombinant DNA Advisory Committee (RAC), where they led to recommendations for changes in the Guidelines. All meetings of the RAC have been announced in advance in the FEDERAL REGISTER, have been open to the public, and have been attended by many nonmembers.

The NIH is sensitive to the need for all concerned to have access to the advisory deliberations contributing materially to the substance and use of these Guidelines. Ordinarily, such meetings will be open to the public and announced in advance in the FEDERAL REGISTER. We have become aware that publication in the FEDERAL REGISTER is not sufficient notice for many, and the *Recombinant DNA Technical Bulletin* and other media will be used whenever possible to supplement announcements of meetings and disseminate reports emanating from them. NIH will also continue its publication of all commentary, transcripts of hearings, and other materials relevant to the "public record" of deliberations on the subject of the Guidelines.

Commentators state that the absence of untoward events in five years of experiments with recombinant DNA is not a valid ground upon which to justify the lowering of containment levels.

There is some merit in this objection, but experience to date should contribute to the basis for revision of the Guidelines. When organisms containing recombinant DNA began to be constructed in 1973, it seemed unlikely to most that hazardous organisms would be produced, yet no one knew for sure. No basis for certainty has yet arrived, but some of the fears have justifiably diminished. The results to date have revealed no major biological factor overlooked in the initial analysis that suggests the guidelines should be stricter than they are. Indeed, several separate lines of evidence indicate the probability of hazards to be even lower than originally thought. That no one has become ill is the least impressive of these. More important lines include the following:

1. Numerous analyses and newer data indicating the very low probability that *E. coli* K-12 will establish itself in the human intestinal tract, thus limiting escape of the organisms in numbers sufficient to infect other living things.

2. The now widely made observation that organisms containing recombinant DNA compete very poorly for survival as compared with organisms not containing recombinant DNA. This was an anticipated finding (see October 1977 Environmental Impact Statement) but has now been documented in various instances. It is true even under laboratory conditions designed to be optimal. Only when the growth medium for the *E. coli* cells containing recombinant DNA is specifically designed to impose selective pressure on the recombinant organisms do they outgrow "Natural" competitors. (Selective pressure could be imposed, for example, by the presence of an antibiotic to which the recombinant organisms are resistant but the natural competitors are sensitive.)

3. The repeated observation that genes of higher organisms, introduced into *E. coli* by shotgun experiments, are not generally expressed. Many of the concerns about possible hazards center on the ability of a host cell to synthesize a foreign protein that might be detrimental to an organism with which the host cell comes into contact.

One correspondent said that assigning a higher degree of containment to organisms that are phylogenetically closer to man is unjustified, with the possible exception of clones capable of harboring viral sequences. The correspondent noted that "even if the cloned DNA were highly homologous to human DNA, how is it envisioned that when carried in a bacterial host it would somehow be more dangerous to man than a non-homologous DNA?" The commentator went on to state that the "production of pharmacologically active agents will clearly not depend upon evolutionary similarity to man" and that in fact such products will likely be specified by lower organisms.

In responding, I must note that a primary concern in the original assignment of containment levels was the possibility that viruses capable of propagating in human tissues could contaminate the DNA. The concern is greatest when the DNA donors are primates or other mammals, and so, for these, higher containment levels are provided.

A secondary consideration involves the possibility that the recombinant DNA may itself transform the host. The likelihood of such DNA integrating into the human genome, and consequently undergoing replication and expression, is directly related to the extent of homology between the foreign and host DNAs.

Another reason for making distinctions on the basis of phylogenetic relatedness is that the more closely related the species, the more likely that polypeptide hormones or related proteins would be pharmacologically active.

A more extensive discussion of the issue of phylogenetic relatedness is given in the Environmental Impact Assessment (FEDERAL REGISTER, July 28, 1978, pp. 33102-33104). This matter lies in a crucial area of risk analysis and will undoubtedly continue to be subject of both further debate and improved understanding in the coming months.

Commentators discuss a number of scientific "fears where there remains reason for caution," including that the virulence of *E. coli* may be increased by recombinant DNA, that recombinant plasmids might be transferred to more virulent strains of bacteria, and that bacteria or viruses containing recombinant DNA could cause autoimmune disease.

In reply, I note that these issues are discussed extensively in the proceedings of the Falmouth Conference (*Journal of Infectious Diseases*, May 1978) and in the EIA of July 28, 1978 (FEDERAL REGISTER).

At the Falmouth conference, evidence was presented on the attempts to make *E. coli* K-12 pathogenic. Even the introduction of *Shigella* genes into *E. coli* by nonrecombinant DNA techniques failed to produce a pathogenic organism having any phenotype suggestive of *Shigella*. There was concensus of all participants at Falmouth that *E. coli* K-12, could not be converted into an epidemic pathogen by recombinant DNA techniques.

There are great safety differences between *E. coli* K-12, an attenuated laboratory strain, and wild-type *E. coli*, as discussed in the EIA.

For an EK2 host to be certified as such, "no more than 1 in 10^8 host cells should be able to perpetuate a cloned

DNA fragment under the specified nonpermissive laboratory conditions designed to represent the natural environment, either by survival of the original host or as a consequence of the transmission of the cloned DNA fragments."

A concern expressed by the commentators is that plasmids containing recombinant DNA might be transferred to other, wild-type organisms in the gut. Some appropriate risk-assessment studies concerning this possibility are being carried out. However, the Falmouth report and tests of EK2 host-vector systems present the following data to indicate that the probability of such transfer of the plasmids is extremely low:

1. H.W. Smith, looking specifically for transfer of a conjugative plasmid from *E. coli* K-12 to normal gut flora, could find no evidence that transfer occurred (Falmouth report, pages 655-660). For biological containment to be breached, transfer of a conjugative plasmid to *E. coli* K-12 would have to occur to be followed by transfer of the poorly mobilizable recombinant plasmid from *E. coli* K-12 to other organisms. (Conjugative plasmids themselves are not allowed to be used as vectors.)

2. Gene transfer *in vivo* greatly increases with colonization by both donor and recipient organisms, and colonization by *E. coli* K-12 in general and x1776 in particular is very rare.

3. Mobilization of the plasmids used in recombinant DNA experiments is extremely low, even under optimal *in vitro* conditions.

4. Transfer of the recombinant-containing vector would require a triparental mating *in vivo*, which even under the most favorable of *in vitro* conditions is not a high-frequency event. Such transfer has not been observed *in vivo*.

5. One commentator suggests that transduction might be an important mode of gene transfer. "Generalized transduction" by phage lambda does not occur. Generalized transduction by phage P1 is a low-frequency event (less that $1/10^8$ infected organisms are transduced for a particular marker) under the very best of *in vitro* conditions.

Additional information on plasmid transfer may be found in the Environmental Impact Assessment (FEDERAL REGISTER, July 28, 1978, p. 33123) and the previous October 1977 Environmental Impact Statement, both of which consider the possibility of transfer of foreign DNA from *E. coli* K-12 as well as the ability of *E. coli* K-12 to survive and spread in nature. As noted in both these documents, the maximum probability for transmission of nonconjugative plasmid vectors from *E. coli* K-12 was estimated at "less that 1 to 1016 K-12s surviving per day in the intestine of warm-blooded animals. The probability is even lower in sewers, sewage treatment plants, and waterways." The EIA further states that *E. coli* K-12 survives poorly and is outcompeted by wild-type enteric bacteria.

The concern expressed by the commentators about the possibility of autoimmune disease will only prove true if a series of events occurs. The very low probability of the establishment of *E. coli* K-12 containing recombinant DNA in the intestinal flora is discussed above. In addition, the inserted eukaryotic gene must be transcribed, translated, and transported to a place where it can induce an immune response. These steps are highly unlikely to occur.

RISK ASSESSMENT

NIH is supporting a number of risk-assessment activities. The Rowe-Martin polyoma experiments are discussed elsewhere in this document. In addition, intramural NIH scientists are collaborating with scientists from other institutions testing the virulence in mice of *E. coli* K-12 containing "shotgun clones" of recombinant DNA derived from other species.

A number of contractors of the National Institute of Allergy and Infectious Diseases are testing the biological containment capabilities of various derivatives of *E. coli* K-12. Some are testing the survival and capacity of plasmid and phage vectors to be transmitted to secondary bacterial hosts in the gastrointestinal tract of mice and man. Others are assessing these parameters in model sewage treatment systems and in situations simulating accidential spills and other types of accidental release of the organisms from experimental procedures.

In addition, investigators proposing systems to be certified by NIH as HV1 or HV2 must perform certain specified tests on these systems relevant to their survival and transmission properties. It is also anticipated in the event that investigators request exceptions to the prohibitions for specified clones, NIH will request substantial risk assessment experiments to be performed to evaluate claims of safety.

SPECIFIC CONCERNS

In addition to their general remarks about the experimental section of the Guidelines, many commentators raised questions about the containment levels set for specific experiments. Others suggested clarifying language for certain sections. I have taken all of these recommendations under consideration. In some instances I have concurred and the Guidelines reflect the change. In others I have decided not to act or have deferred actions pending futher analysis and discussion by the Recombinant Advisory Committee. In all cases I have attempted to respond and to explain the decision.

Section III-A-1: Shotgun Experiments

Comments from respondents on this section of the Guidelines reflected diametrically opposed points of view. Some commentators questioned the rationale for lowering of containment levels for shotgun experiments.

Other correspondents took a different view and requested that NIH further reduce the containment level for shotgun experiments. One advanced the argument that "these pieces of DNA in *E. coli* cannot be more dangerous than their original source."

I have decided to retain those levels of physical and biological containment described in the proposed revised Guidelines. I believe the specified containment levels represent a prudent, albeit most conservative, response to the hypothetical hazards. Rationale for them is presented in the July 28, 1978, Decision document and Environmental Impact Assessment.

Risk analysis by NIH is continuing. One important area of analysis involves the appropriateness of higher containment levels for shotgun experiments, with the tremendous dilution of potentially harmful genes, in contrast to purified clones that have been "engineered" for efficient transcription and translation of DNA inserts.

Section III-A-1-a. Eukaryotic DNA Recombinants Including Primates, Other Mammals, and Birds

Twelve commentators, the largest number of comment on a single issue, wrote to express their views on the limitation of P2+EK2 under the proposed revised Guidelines for the cloing in *E. coli* K-12 of shotgun DNA from primates, other mammals, and birds. All requested that the option of P2+EK2 or *P3+EK1* be offered.

One group argues that to restrict cloning of these classes of DNA to P2 + EK2 is inconsistent, since many viral genomes could be cloned at either P2 + EK2 or P3 + EK1. Other respondents pointed out that use of P3 + EK1 conditions would provide adequate containment and would permit the inclusion of lysogenic lambda systems, which cannot be employed in an EK2 system. One stated that propagating DNA fragments in EK1 host-vector systems permits a 5-10 times greater yield of DNA than in an EK2 system. "Thus the advantage of EK2 containment should be weighed against the necessity of handling much larger volumes of cells."

I referred this matter to the RAC at their October 30-31, 1978, meeting. The RAC advised that the phrase "or P3 + EK1" be added to Section III-A-1-a-(3) (i.e., for DNA from birds) and

this has been done. For Sections III-A-1-a-(1) and III-A-1-a-(2) (DNA from mammals), the RAC recommended addition of the phrase "or P3 + EK1 with a non-mobilizable plasmid." Because the term "non-mobilizable plasmid" is not clearly defined, I am not accepting this recommendation at present, pending further review at the next RAC meeting.

Section III-A-2-a. DNA From Virsus of Eukaryotes Into E. Coli K-12

There was considerable comment about various aspects of Section III-A-2-a, extending from general concerns about the reduction of containment levels from viral inserts to detailed and specific recommendations for clarification of certain phrases.

Several correspondents objected to the general relaxation of containment levels for the cloning of viruses. One stated that although the Ascot conference concluded that "cloning of the whole or any part of a viral genome must logically be less dangerous than working with the virus," his view is just the opposite. The arguments presented by this correspondent are (1) whole virus can elicit the production of antibodies, (2) whole virus with its protein coat is subject to a biological barrier which limits infection across species lines, and (3) whole virus is eliminated from the body after infection. In the view of this correspondent, all of these protective devices are subverted by cloning viral genes in a microorganism that may become established in the intestinal tract. He is also concerned that the Guidelines are not sufficiently stringent for cloning subgenomic DNA fragments of viruses. Another respondent indicated that belief that containment experiments involving animal-cell transforming viruses were substantially reduced, based on the supposed inefficiency of infection by naked DNA. She continued by stating that the decision to lower containment did not take into account the results of the Rowe-Martin risk-assessment experiments with polyoma DNA, which showed that naked polyoma DNA when injected into the bloodstream of mice caused a low-level infection.

The recommendations of the Ascot Workshop (Appendix E to the Environmental Impact Assessment), the subsequent Working Group review (Appendix F to the EIA), and the subsequent RAC review took into account the concerns of correspondents about viral containment, but nevertheless recommended lowered containment levels based on the conclusion that cloning of viruses or their fragments in *E. coli* could be no more dangerous than working with the intact virus. The containment levels were set accordingly. The three reasons cited above as to why the cloned virus DNA might be more dangerous than the whole virus apply only to the first infected cell. The DNA would produce disease only if it became virus and spread; thus, the situation becomes the same as the usual virus infection. This possibility was thoroughly considered at Ascot, and is in the summary report of that meeting. Also, the existence of a subgenomic fragment precludes virus production and so effectively prevents the spread of infection.

The Rowe-Martin risk-assessment experiments (still in progress) are designed to compare the infectivity of a recombinant molecule containing polyoma DNA with that of nonrecombinant polyoma DNA and of whole polyoma virus. To date, there are no data available from these experiments which would lead me in any way to revise the judgements of the meetings cited above.

In response to the concern expressed about naked DNA, there is a significant difference in level of infectivity between naked DNA and whole virus particles; naked DNA is much less infectious than the virus. For additional discussion of naked DNA, see part I of this document.

A correspondent stated that there should be some definition as to whether a DNA virus is a transforming or nontransforming virus. To clarify this, a new footnote (37A) has been added to Section III-A-2-a-(1)-(b).

A correspondent pointed out that there are places in Section III-A-2-a where the word "purified" appears without referencing to Footnote 38. This has now been corrected by inserting reference to Footnote 38 where necessary, and inserting the phrase "subgenomic segments that have not been purified to the extent required in Footnote 38" at other places.

A correspondent discussed "EK1CV." defined in Footnote 40 as the "the use of an EK1 host and a vector certified for use in an EK2 system." He points out that certain EK1CV systems provided containment comparable or almost comparable to EK2, while others are only slightly better than EK1. This is true. However, in all cases the level of containment is higher than EK1. The cases in the Guidelines where EK1CV containment is specified as an option were so recommended by the RAC on the basis of the recommendation of the April 6-7, 1978, Virus Working Group (Appendix F to July 28, 1978, Environmental Impact Assessment).

Section III-A-3. Lowering of Containment for Characterized or Purified DNA Preparations and Clones

As in many other sections of the Guidelines, commentators have expressed their opinions in both general and specific terms. A commentators states that there is no information at present to "show any hazard deriving from recombinant DNA or organisms harboring such DNA * * *. In particular, it would seem quite clear that characterized cloned eukaryotic DNA elements in *E. coli* pose no conceivable hazard." Pursuing this line of reasoning, the commentator argues for elimination of regulation and, in particular, suggests that "consideration be given to a change in the Guidelines so that institutional biohazard committees could be empowered to exempt characterization clones from further regulation."

The proposed revisions in the Guidelines empower the IBCs to give approval for a single-step reduction in physical or biological containment upon receipt of evidence of characterized of a clone and its freedom from harmful genes. Further reductions, or cases involving primate DNA or lowering of containment levels below P1 + EK1, require prior approval by NIH. I do not believe it prudent to accept the commentator's recommendation at this time.

Two comments were received on the criteria for the terms "purity" and "free from harmful genes." Once commentator expressed concern over the inadequate definition of these terms. He believes they are not defined with sufficient precision to guarantee uniform decisions, particularly when the authority to lower containment by one step is left with the IBC. The commentator suggests more rigorous criteria for purity (other than 99 percent) and a broader definition of "harmful gene" to include the concept "that genes which might not be harmful when expressed in their original organism could indeed be harmful if expressed out of context in an unrelated organism."

The other correspondent discussed Footnote 41 which requires that the "desired DNA represents at least 99 percent (w/w) of the total DNA in the preparation" before it may be considered "purified." He stated: "Its adoption reflected the supercautious mood prevalent at that time rather than a clear-cut scientific judgement. In my view, requiring that a DNA fragment should be 90-95% pure (as judged by at least two different analytical procedures) to remove it from the shotgun classification is more realistic and no less safe. Requiring that a DNA fragment be >99 % pure prior to cloning asks for the most stringent and detailed documentation without any real advantage."

The term "purity" is very explicitly defined in Footnote 41. The requirement is that the desired DNA must represent at least 99 percent (w/w) of

the total DNA in the preparation. In addition, at least two biochemical or physical procedures are required for verification of purity.

Footnote 3 gives guidance to the IBCs on many factors to be considered before deciding that DNA recombinants are "free of harmful genes." Further specificity seems unwarranted. I believe that to broaden the definition to include the concept of "harmful" when a gene is expressed out of the normal physiological context would be contrary to the intent of Footnote 3. In considering this issue, I have noted that in the proposed revised Guidelines, different terms are used: i.e., in Section III-A-3, "and the absence of harmful genes established"; in Section III-A-3-a, "are free of harmful genes"; in section III-A-3-b, "and there is sufficient evidence that it is free of harmful genes." These have all been changed (also in Footnote 3 and Section I-D-6) to "and the absence of harmful sequences established." I have also decided that the 99 percent criterion should be retained in the present revision of the guidelines; but this point will be reconsidered by the RAC as a possible item for future revision.

Section III-B. Experiments with Other Prokaryotic Host-Vectors

Several correspondents addressed the use of hosts other than *E. coli* K-12. They pointed out that many experiments with such hosts are "inadvertently prohibited," and suggested wording to allow experiments in hosts other than *E. coli* K-12 which do not meet the criteria for HV1.

In the proposed revised Guidelines, experiments with prokaryotic hosts other than *E. coli* K-12 fall into the following classes: (i) Self-cloning, exempted under the exemption I-E-3; (ii) return of DNA segments to non-HV1 host of origin, Section III-B-2; and (iii) use of HV1 systems, Section III-B-1. I agree that there are many safe experiments which fall into none of the above three classes but which should be allowed under specified containment levels. The proposed revised Guidelines, at the beginning of Section III, stated, "• • •(or the assignment of levels to experiments not explicitly considered here) may be expressly approved by the Director, NID, on the recommendation of the Recombinant DNA Advisory Committee (RAC)." This language has been retained in a slightly modified form in the final Guidelines. In addition, similar language is now repeated in a new Section III-B-3 and at the end of Section III-C-5.

A specific example of this type of problem was provided by a commentator who cited experiments he would like to perform involving recombinant DNA from *Bacillus popilliae*, a pathogen for the Japanese beetle, and *Bacillus thuringiensis*, a pathogen of pest caterpillar larvae. He asked for clarification of what containment levels would apply under the proposed revised Guidelines.

The experiment could be considered under several different provisions. If data are submitted on natural exchange of DNA between *B. popilliae* and *B. thuringiensis*, these organisms could be listed in a future version of Appendix A as falling under exemption I-E-4. Or under the new paragraph III-B-3 which has been added to the Guidelines, containment levels could be set for these experiments.

Section III-C. Experiments with Eukaryotic Host-Vectors

A general issue raised by one respondent concerns the stipulation that some experiments will be assigned containment levels on a case-by-case basis. The commentator is concerned that this approach ignores the need for minimumm standards which can serve as a guide for research workers.

I believe that the case-by-case analysis prescribed for many experiments involving the employment of viral DNA as a vector reflects the caution exercised over the use of such DNA. Each such experiment is thus prohibited until the RAC has had a chance to weigh the scientific evidence and propose whether the experiment should proceed and, if so, to assign appropriate physcial and biological containment levels.

I have accepted several other recommendations for changes in this section. Two commentators offered new language for the section dealing with requirements for the employment of defective adenoviruses as cloning vectors. They noted that new mutants of Ad5 or 2 in which the entire transforming region has been deleted have recently been isolated. These mutants can only be propagated in adenovirus-transformed cells. The commentators suggested that the language in Section III-C-1-c-(1)-(a) be generalized to state: "Human adenoviruses 2 and 5, rendered unconditionally defective by deletion of at least two essential genes, with appropriate helper, can be used under P3 conditions to propagate DNA sequences from • • •." I believe this is justified, and the Section has been modified by changing the word "capsid" to "essential."

A correspondent stated that Section III-C erroneously equates nonproductive infections with nonpermissive cells. He pointed out that in certain situations nonproductive infections may result from infection of permissive cells. I agree. Accordingly, the phrase "to transform nonpermissive cells in culture" has been eliminated at a number of places in Section III-C, and more appropriate language has been substituted.

The same correspondent pointed out that in Section III-C the word "intact" is not appropriate because as soon as a foreign sequence is introduced, the viral DNA is no longer intact. I agree. The wording in the relevant sections has been changed from "intact" to "whole."

Section III-C-2, Invertebrate Host-Vector Systems in Which Insect Viruses Are Used to Propagate Other DNA Segments. Section III-C-3, Plant Viral Host-Vector Systems. Section III-C-4, Plant Host-Vector Systems Other than Viruses

I have considered the comments for these three sections in a single group.

A witness questions "the necessity for EPA registration of an entomopathogenic organism in lieu of simply meeting the criteria of EPA for a temporary exemption from a requirement of tolerance in the environment."

In the proposed revised Guidelines published in the FEDERAL REGISTER on September 27, 1977, "baculoviruses which have been registered by the Environmental Protection Agency" are specifically discussed in the section dealing with invertebrate host-vector systems in which insect viruses are used to propagate other DNA segments. The writer is apparently addressing this section and requesting that the EPA registration not be required but merely "the criteria of EPA for a temporary exemption from a requirement of tolerance in the environment." The analogous section (III-C-2) in the proposed revised Guidelines published in the FEDERAL REGISTER on July 28, 1978, does not in fact refer to EPA registration as a specific criterion. It indicates that experiments in which insect viruses are used to propagate other DNA segments will be evaluated on a case-by-case basis by the Recombinant Advisory Committee. Information required for a judgment includes host range restrictions, and infectivity, persistence, and integration of the viral DNA. Data submitted by the requesting investigator on whether EPA has registered a given insect virus or whether it meets the EPA criteria for a temporary exemption from a requirement of tolerance in the environment will be considered by the RAC.

The same witness also questioned the validity of the statement in Section III-C-3 that "the plants should be grown under P1 conditions—that is, in either a limited access greenhouse or plant growth cabinet which is insect-proof" and suggested substitution of the term "insect-restrictive" rather than "insect-proof," since the latter term implies higher containment. I

concur with the recommendation and have made the change.

On the other hand, I do not agree with the opinion of the correspondent who questioned the relevance of P1 or P2 containment conditions to experiments in which recombinant DNA is cloned in higher plants. The correspondent believes that higher plants containing nonviral recombinant DNA should not require any containment. The proposed revised Guidelines (pages 33082 and 33084 in the FEDERAL REGISTER July 28, 1978) specifically define special P1 and P2 conditions for work with plants. I do not believe that recombinant DNA work with higher plants should now be done with no containment at all.

Finally, I have considered the request of two correspondents discussing employment of the tumor insertion plasmid (Ti) of *Agrobacterium tumefaciens* as a cloning vector. They suggest adding the following sentence to Section III-C-4: "Inoculation of hosts with HV1 approved *Agrobacterium* containing the DNA recombinants requires P2 physical containment." I do not believe inclusion of the sentence is warranted at this time. Data on the system can be submitted to the RAC for approval as an HV1 system. If approval is granted, the RAC at that time can recommend the appropriate containment level.

Section III-D. Complementary DNAs

Two correspondents were concerned over the possibility of eukaryotic DNA being expressed in prokaryotic cells. They noted that genes cloned via a shotgun experiment will probably not be expressed because they retain their intervening sequences and the resulting RNA is not likely to be processed. On the other hand, complementary DNA prepared from messenger RNA could serve in turn as a template for synthesis of the same RNA within the prokaryotic cell. They suggest that a "distinction should be made between eukaryote DNA and cDNA formed from mRNA."

In responding, I must note that containment levels for eukaryotic DNA were developed on the assumption that such DNA, no matter what the source, could be expressed. The proposed Guidelines set the same containment levels for eukaryotic DNA and cDNA formed from functional eukaryotic mRNA. For cloning of viral DNA into *E. coli* K-12, however, there are differences in the containment levels depending on whether one is using the viral DNA itself of cDNA from viral mRNA (see Table III). The probable future uses of cDNA copies of functional mRNAs are discussed in the Introduction and Overview of the Director's Decision (FEDERAL REGISTER, July 28, 1978, pp. 33044 and 33047).

Section III-E. Synthetic DNA

A correspondent argued that the discussion of appropriate containment levels for synthetic DNA that codes for harmless polypeptide products "makes no sense." He asks, "Why is any containment required for a harmless product?" and recommends the following alternative language for this section: "If the synthetic DNA sequence codes for a harmless product or if the synthetic DNA is not expressed *in vivo*, the organisms containing the recombinant DNA are exempt (4) from the Guidelines."

In reply, the term "harmless product" refers to the normal toxicity or pathogenicity of the protein and not necessarily to the remote possibility of its otherwise disrupting the physiological balance of the organism in which it might inadvertently be introduced. I believe that the language of the NIH-proposed revision should remain as published, since the three paragraphs describing containment for synthetic DNA clearly describe three distinct concepts. The provisions of Section III-E are consistent with those of III-A-3 dealing with containment levels for purified or characterized DNA.

IV. ROLES AND RESPONSIBILITIES

RESPONSIBILITIES OF THE INSTITUTION (GENERAL)

Institution

The general responsibilities of the institution are to ensure appropriate review and implementation procedures for all of the institution's recombinant DNA activity that is covered by the Guidelines. Below are a number of general institutional responsibilities that were addressed in correspondence and by witnesses at the DHEW public hearing.

Exercising Institutional Authority. Both groups of commentators stated that the Guidelines should permit the institution to set new requirements beyond those of NIH. In the Guidelines, the institution has this authority, and a provision has been added specifically stating that the institution may establish requirements and procedures for the general implementation of the Guidelines, including additional precautionary steps if deemed appropriate. It should be noted, however, that these Guidelines and the standards they embody are conservative and in no way constitute a minimum set of requirements.

Establishing an Institutional Biosafety Committee. Requirements for membership on the Institutional Biosafety Committee (IBC) drew substantial attention in the letters and at the public hearing. Much of the comment was directed to mandating various representation. Some commentators suggested that a local public health official and a nondoctoral person from a laboratory technical staff serve on the committee. Others recommended mandating community leaders who are "in touch with grass roots attitudes," including "environmentalists." Others suggested that the membership reflect the demographic distribution of the community in which the institution is located. Requirements for membership distribution by age, sex, income level, professional background, and other variables were mentioned. It was suggested that at least two members be custodial or janitorial workers. Others recommended that there be at a minimum one physician trained in infectious diseases, one epidemiologist, and one environmental scientist.

Other commentators and witnesses suggested various ratios of scientists and nonscientists serving on the committee. Some urged that one third of the membership represent "the interest of the community" and another third "scientific disciplines related to risk assessment." It was also suggested that nominating procedures be specified for selecting community representatives.

On the other hand, some commentators believed that the proposed revision was presumptuous in mandating lay representation on this committee, especially when the university may already have several lay committees for oversight.

Others suggested that the minimum membership for an IBC be raised from five to seven. The minimum of five members is recommended to take into account small universities with few projects. In these and many other cases, five is sufficient, and it remains as the minimum. Membership recommendations in the revised Guidelines attempt to balance professional expertise with members who represent the interest of the surrounding community. As pointed out by one correspondent, however, the IBC, in contrast to human-subject committees where broad concepts of social and ethical values are considered, is in large part an expert committee whose essential function is to evaluate research protocols in respect to containment levels, using the explicit instructions of the Guidelines. Rigid quotas are not necessary. Indeed, many small academic institutions would have considerable difficulty meeting specified demographic requirements. The IBC criteria are flexible to permit the institution to select a committee capable of fulfilling its responsibilities.

The DHEW Committee carefully reviewed all the comments and considered at great length membership requirements for the IBCs. On balance, it was decided that the interest of the surrounding coummunity could be

served, as one commentator suggested, by "at least two members." In addition, at least 20 percent of the committee shall not be affiliated with the institution and shall represent the interest of the surrounding community with respect to protection of the public health and the environment. Moreover, nomination procedures need not be specified, but should be left to the discretion of the institution for the selection of these members.

With respect to conflict of interest, some commentators recommended that IBC members be prohibited from any direct involvement in recombinant DNA or closely related research unless the member is a laboratory worker. The conflict-of-interest provisions in the Guidelines respond to these concerns while reflecting the paramount need for relevant scientific competence on the IBCs.

A commentator stated that "peer review does not adequately protect the public," citing instances of noncompliance with the Guidelines at two NIH grantee institutions. It should be noted that the two cases in point involved administrative violations and presented no risk to the public health or the environment.

Some of the commentators from the private sector expressed concern that the financial conflict-of-interest statement required in the Guidelines might be interpreted as denying IBC membership to any member of a company. Others felt that a requirement for public members woud present problems of protecting confidential information. However, at a meeting of the DHEW Committee and representatives from the Pharmaceutical Manufacturers Association, it was agreed that public members could and do serve on the committees. Some are asked to sign agreements to honor confidentiality of proprietary and patent information.

Health Surveillance. This area was one of deep concern to some witnesses and correspondents. Witnesses at the September 15 hearing made several suggestions concerning medical surveillance, and correspondents suggested that the term "medical surveillance" be changed to "health-risk surveillance" or "health surveillance." That suggestion has been adopted in the Guidelines.

Several commentators and witnesses urged that health surveillance programs be required in the Guidelines. Concern was expressed that without such a requirement different standards and different programs would result. In addition, there were many suggestions from commentators, including the Occupational Safety and Health Administration (OSHA), about what should constitute a health surveillance program—for example, complete medical histories, periodic medical checkups, and serial serum samples. It was recommended that laboratories be required to keep official OSHA health and safety log forms, and that records be kept of all agents use, all modified organisms created, and all laboratory-acquired illnesses.

Several commentators also called for a clearinghouse, to be established at the Federal level, at which copies of all health surveillance plans and records would be filed. It was urged that NIH maintain such data, including records of workers in laboratories using recombinant DNA techniques, with particular regard to instances of possible work-related illness. There were also several suggestions for a national epidemiologic monitoring and surveillance program to be supported by DHEW. Such programs might, as one commentator suggested, promote national standards for health surveillance specific for each class of organisms and group of experiments. And finally, there were suggestions for ongoing epidemiologic and biostatistical analysis of data as they are accumulated to permit early detection of trends.

I reviewed these issues in the Decision document accompanying the proposed revised Guidelines as published in the FEDERAL REGISTER July 28, 1978. As I noted in that document, the issue of medical monitoring is one of considerable interest to NIH and is not unique to recombinant DNA research. The "state-of-the-art," however, is primitive in terms of effective monitoring of workers' health generally, and particularly in recombinant DNA research, where there is no known hazard.

One commentator noted that the Cambridge, Massachusetts, city ordinance for recombinant DNA research requires the institution, as part of its health surveillance responsibility, to monitor survival and escape of recombinant DNA organisms in each laboratory worker engaged in this type of research, as by the testing of intestinal flora. Intestinal flora sampling is being undertaken at MIT. NIH will follow the MIT program closely. This in not the time, however, to propose extension of that experiment to general practice.

We recognize the need to aid the institutions as much as possible in this important area. The laboratory Safety Monograph provides extensive detail and guidance. It suggests monitoring illnesses, collecting serum samples, and keeping a register of agents handled. Moreover, the Guidelines now require the institution (rather than the principal investigator) to determine, in connection with each project, the necessity for health surveillance of relevant personnel and to conduct a health surveillance program appropriate to the project. And the Memorandum of Understanding and Agreement will include reference to health-surveillance programs associated with the project.

In response to the calls for a national clearinghouse, it should be pointed out that the NIH Office of Recombinant DNA Activities (ORDA) has been designated in the Guidelines to receive, review, and maintain certain medical and accident information. Through ORDA, NIH will have a collection of essential data which should provide the ability to discern if certain experiments result in unique health problems. It is emphasized, however, that for any health surveillance to be truly effective, it must be conducted at the local level.

RESPONSIBILITIES OF THE INSTITUTION (SPECIAL)

The special responsibilities of the institution include establishing general policies, appointing the Institutional Biosafety Committee (IBC), appointing a Biological Safety Officer (BSO) where required, and reviewing and implementing procedures applicable to the submission of the Memorandum of Understanding and Agreement (MUA). A number of commentators and witnesses addressed these requirements.

One commentator recommended that the signature of an institutional offical not be required on the MUA (in Appendix C of the July 28 revision), but that the IBC chairperson should represent the institution. The signature of an institutional official on the MUA is requisite, for that individual is authorized to act for the institution and assume on its behalf the obligations imposed by the Guidelines. If the institution so wishes, however, it may designate the IBC chairperson as the responsible official for MUAs that do not require prior NIH approval. This is newly noted in the Guidelines and the Administrative Practices Supplement (APS), which now incorporates Appendix C.

The correspondent also recommended that MUAs for fellowships, as found in Appendix C, be deleted as an unnecessary duplication of effort. This recommendation is sound, for it is duplicative to require an MUA when the projects are registered. Thus, MUAs will not be required with fellowship applications.

Another correspondent called for clarification of the difference, if any, between the IBC's procedures for review of NIH-funded and non-NIH-funded projects. The information required for NIH- and non-NIH-funded projects in an institution receiving NIH support for recombinant DNA research is similar. Further information on the requirements has been included in the APS. For purposes of IBC

review and monitoring responsibilities, there should be no distinction between NIH- and non-NIH-funded projects.

Another commentator urged that the Guidelines give greater detail on the types of protocol changes for which a new or revised MUA must be sent to NIH. Information proviously contained in Appendix C has now been added to the Guidelines to clarify this point, and further information is contained in the APS.

Another commentator suggested that the institution be required to notify a local Health Systems Agency upon filing an application for Federal support of recombinant DNA research. This is not applicable to HSA responsibilities under section 1513(e) of the PHS Act and therefore is not mandated.

Another correspondent requested that Appendix C be mandated. The test of Appendix C, now in a supplement to the Guidelines (the APS), has been extensively rewritten, and many of its features have been incorporated in the Guidelines for purposes of clarification. I agree that the provisions now in the Guidelines should be mandatory.

Institutional Compliance. A commentator challenged the right of NIH to require an institution to hold that all principal investigators, irrespective of source of funding, must follow the Guidelines. This requirement, however, is vital to the maintenance of uniform standards and is therefore retained. On the other hand, research supported by another Federal Agency need not be registered with NIH when that agency maintains a registry and provides NIH with essential information.

Another commentator suggested delegating responsibilities for all enforcement of the Guidelines to the institution (IBC), with ORDA receiving periodic reports from the committees on the research they are regulating. There are several reasons such a course would be unwise at this time. Exercise of any discretion is a new responsibility for the IBC's. Uniformity and expertise must be demonstrated by verification through NIH review. A great deal of standard-setting, necessarily central at present, is yet to be done through case-by-case analysis.

One commentator requested that the NIH notify both the IBC chairperson and the institution when it was reviewed each action of the IBC according to the imformation submitted on the MUA. This, I believe, would strengthen coordination of compliance efforts. The final Guidelines accordingly require the double notification.

It was also suggested that NIH provides a statement that it has certified the institution and finds it to be in compliance. This request is related to requirements in State regulations that go beyond the Guidelines. However, NIH plans to provide official documentation to institutions in States requiring such information. The subject will be further treated in the APS.

Another commentator urged NIH to devise a system to protect those who report possible violations. This issue was reviewed in my Decision accompanying the proposed revised Guidelines (FEDERAL REGISTER, July 28, 1978, p. 33065), where I noted that grievance procedures for workers under the Guidelines were not considered necessary because OSHA rules and regulations already provide such a mechanism. However, witnesses at the September 15 hearing and comments from OSHA state that the Occupational Safety and Health Act does not cover employees of State and local governments unless the State operates under an OSHA-approved State plan covering health and safety practices and grievance procedures. Only 23 States currently have such plans. But other States presumably have similar statutory protection, and it would be presumptuous of NIH to attempt to detail specific grievance procedures in all jurisdictions. The Guidelines require the reporting of violations and allow the reports to be made to NIH by anyone. The institutions, I believe, will accept such reports in a positive light and as an important aid in maintaining compliance with the NIH standards.

Institutional Biosafety Committee (IBC)

The principal functions of the IBC are to review and oversee all recombinant DNA projects with respect to compliance with these Guidelines and to advise the institution and ORDA whether the proposals and the research so comply. A number of issues concerning IBCs were addressed by the commentators and witnesses at the September 15 hearing, including delegation of authority to the IBCs, public representation on the committee, and public access to its proceedings.

Delegation of Authority. Several correspondents and a number of witnesses at the September 15 public hearing took exception to the delegation of authority to the institutions and their IBCs to act on certain experiments without *prior* NIH approval. One witness noted that there has been a 4 to 15 percent error rate by the IBCs. He also noted that NIH review did not entail inordinate delays, citing the usual review at ORDA as taking only 4 to 5 days. He urged that NIH retain the present two-level system of review requiring prior NIH approval for all projects. The data here do not take into account additional referrals of MUSs between ORDA and various NIH Institutes supporting such research. These have introduced delays of may days or weeks in processing. Other commentators recommended quite the opposite—that greater latitude be given the IBCs to assign containment levels for experiments.

The reason for the delegation of authority is extensively discussed in my Decision and the Environmental Impact Assessment accompanying the July 28 publication of the proposed revised Guidelines. As stated in the Decision document, the increased responsibility of the institution is in response to comments calling for a simpler administrative process and more local responsibility. It is also a recognition of the practical requirements for enforcement of standards for use of such highly varied and complex technology in many institutions spread over a vast area. As stated by the House Committee on Interstate and Foreign Commerce in its report of March 28, 1978, on the Recombinant DNA Act: "* * * the appropriate portions of the administrative requirements of section IV of the NIH Guidelines are a reasonable model upon which the Secretary could base administrative regulations. In particular the current practice in the NIH Guidelines of delegating to local biohazard committees most of the responsibility for the inspection of the facilities and the approval of the specific safety requirements appropriate to each project or activity is an effective and relatively inexpensive administrative mechanism." Thus, the delegation of increased responsibility at the local level is not primarily to facilitate an increased volume of research, as suggested by a commentator, but rather to place this function at the most appropriate location for initial enforcement of the Guidelines. It should be noted, however, that MUAs, before going to ORDA, go to the NIH Institute funding the research, and there have been delays of days or weeks at this level, adding substantially to the time required for processing. We will consider means to simplify procedures so the ORDA can respond in a timely fashion to the institutions.

The DHEW Committee carefully considered the issue of prior NIH approval. On the basis of that review, the Guidelines now specify the circumstances in which prior approval is required, with greater detail provided in the APS. In addition to the five categories of experiments requiring prior approval in the NIH proposal, prior approval is now required, on the recommendation of the DHEW Committee, for the first project to be conducted by an institution and the first project in a facility at P3 containment.

It should be emphasized that while the delegation to the IBCs permits initiation of all other research at the local level, the NIH review and approval of all research under the Guidelines will continue as before. All protocols not found to be in conformance must be modified. Given the slowly increasing sophistication of investigators and IBCs alike, plus the provision in the Guidelines of explicit standards for performance of their duties, I am confident that this delegation will in no sense present risks to the health or the environment.

It should also be noted that some commentators still regard proposed administrative procedures as "excessive and disproportionate when measured against the perceived risks." They are especially concerned that the work of the IBCs is taxing the human and financial resources of the institution. That a burden is placed on the local institutions cannot be denied, but the responsibility is better delegated than retained at the Federal level. As we learn more, there will presumably be less and less need for formality and centralized review in the governance of this research. In anticipation of probable decentralization with time, creation of the local capability must begin without delay.

Another commentator urged that the Guidelines be extended to all hazardous biological research. As stated in my Decision of July 28, I do not believe we can or should extend the Guidelines to other research at this time. However, the entire area of laboratory safety is of prime concern to NIH and the subject of constant review and attention. NIH activities in this area are described in the Environmental Impact Assessment published with the Guidelines as proposed in July. It should be noted that some IBCs, as one correspondent pointed out, assume the added duty of monitoring work with known pathogens that is not related to recombinant DNA technology.

In view of the delegation, some commentators urged that there be more financial support for the operations of the IBC. It was recommended that NIH require some percentage of the overhead charged on recombinant DNA research proposals to be earmarked for operation of the IBCs.

Concern has been expressed in the past about the cost of the IBC operations. As stated before, NIH already pays for the operations of such committees through reimbursement of so-called indirect costs of research. I do not believe there is need at this time to separate them from other indirect costs of the institutions.

Reduction of Containment Levels. A number of commentators and witnesses questioned the authority of the IBCs to lower containment requirements for certain experiments. On the other hand, many believe the IBCs should be authorized both to reduce and to raise containment levels. It should be understood clearly that the IBCs' authority to lower containment levels is quite limited and governed by strict standards and procedures set forth in the Guidelines. NIH is notified of all such discretionary actions. It will review them and require that any failures to come up to the standards of the Guidelines will be corrected.

Specifically, the IBC can reduce containment levels only for experiments using purified DNA and for characterized clones. Standards and procedures for the former action are stated in Section III-A-3-a of the Guidelines and in Footnote 41; those for the latter action, in Section III-A-3-b and in Footnote 3. Standards for both actions appear also in the IBC section of part IV of the Guidelines and in greater detail in the Administrative Practices Supplement. Further, it should be noted that NIH approval is required for any lowering of containment levels below P1 + EK1, or by more than one step, or for experiments involving primate DNA.

Specific authority is granted to the institution (Section IV-D-1) to establish requirements deemed necessary for the implementation of these Guidelines. The IBC, then, can raise containment levels. The national standards, however, are very conservative, and in my view, to raise them generally or for characterized clones and purified DNA is unwarranted.

Appeals. Several commentators advocated, in light of the authority delegated to the IBCs, procedures for "appealing a decision of the local IBC against a project or against a certification of facility." The Guidelines do not prescribe an appellate mechanism. A full partnership of investigators and their institutions is intended in maintaining compliance with the Guidelines. The investigators and the IBCs must not be cast in adversary roles, and NIH will make every effort to promote their cooperation. We will be available on request to provide technical advice and consultation with principal investigators and institutional committees alike.

Emergency Plans. The IBC has responsibility to review and approve emergency plans. A number of commentators suggested greater detail in the Guidelines on the emergency procedures to be employed, including specification for cleanup procedures to be followed should there be a spill or accidental release of organisms into the environment. Other commentators suggested that the Guidelines set national standards for the handling of emergency spills. Several urged that the biosafety officer at each institution be charged with responsibility for drafting such plans.

The Laboratory Safety Monograph presents guidance on pages 194-196 on procedures to be followed in emergencies. Some of that information is now included in the Guidelines to emphasize its importance. The monograph will be revised further, in response to comments, to provide greater detail and to include emergency numbers at NIH and the Center for Disease Control that can be called on a 24-hour basis. The two agencies will provide consultation and direct assistance if needed. In addition, the Guidelines specify that the institution shall cooperate with the State and local public health departments and report to them any illness or laboratory accident that appears to be a hazard to the public health. And the IBC chairperson is responsible for notifying the institution and NIH, within 30 days, of problems with the Guidelines, violations, or significant research-related accidents or illnesses, unless the chairperson finds that the PI has done so.

Public Access. Several witnesses at the September 15 hearing and many commentators urged greater public access to proceedings of the IBC. The proposed revised Guidelines required that minutes of the IBC meetings be made available to the public upon request. However, there were several suggestions for further requirements. Witnesses urged that the IBC meetings be publicized and open to the public, except for those specifically dealing with proprietary or other confidential information. Suggestions were made to enchance public participation through evening meetings of the committee and the use of lay summaries of research proposals. Procedures were recommended for announcing IBC meetings. Others recommended that all MUAs and reports of inspections be made publicly available.

The DHEW Committee spent a great deal of time reviewing comments about this portion of the Guidelines. In my Decision accompanying the proposed revision of July 28, I noted that possible discussion of proprietary and patentable information often precludes open IBC meetings. I did urge, however, that local committees have open meetings when possible and that they be publicly announced.

In response to the issues raised, and in view of the increased responsibility given to the local institutions, the final Guidelines require, in addition to public representation on the committee, public access to proceedings of the IBC. Institutes are encouraged to open IBC meetings to the public whenever possible, consistent with the protec-

tion or privacy and propritary interests.

In addition, the IBC is to forward to NIH any public comments made on its actions and the committee's response to them. And all IBC documents that NIH must make available to the public, such as the funded research proposals, are also to be made available, upon request, at the local level. These include reports of serious accidents and of problems with and violations of the Guidelines; also all NIH reports to institutions when MUAs (including modifications of ongoing projects) are not in compliance. Likewise, minutes of the IBC meetings and inspection reports will be made available. The intention of the Guidelines in all these changes is to enhance public accountability at the local level.

Biological Safety Officer

There were a number of comments concerning the roles and responsibilities of the Biologial Safety Officer (BSO). Several witnesses at the September 15 hearing recommended that whenever recombinant DNA research is being conducted at an institution, such an officer be appointed and required to serve on the IBC. It was also recommended that the BSO have a full-time position. The Committee considered the role of the BSO at some length.

The Guidelines do specify that all institutions conducting work at the P3 and P4 levels must have a BSO. The officer is required at those levels because the sophisticated equipment and facilities require special abilities. The Laboratory Safety Monograph (p. 191-193) outlines the qualifications and role. But the Guidelines do not mandate such an officer for P1 and P2 work because the potential risk at those levels is minimal and the expertise readily available for laboratory safety. The Committee concurred with this view.

Other commentators recommended that the Guidelines assign to the BSO responsibility for monitoring, keeping records, and health surveillance. The DHEW Committee reviewed the qualifications of BSOs, noting the absence of certification procedures for such a new and ill-defined discipline. Accordingly, it was agreed that certification requirements should not now be stipulated for BSOs and that flexibility should be encouraged to permit a BSO to have responsibilities for such activities as health surveillance. As noted in the LSM, one can call on the environmental health and safety program at the institution to assist in a variety of the duties suggested for the safety officer.

The BSO is responsible for developing emergency plans, and the NIH will provide assistance for program development. But in my view, it is far more sensible at present to begin emergency plans at a local level than to attempt to develop them on a grander scale until any hazards are better understood. Unless the principal investigator has already done so, the BSO is also responsible for providing reports to the IBC and the institution on problems with and violations of the Guidelines and on all significant research-related accidents and illnesses.

Principal Investigator

As stated in the introduction to part IV, safety involving recombinant DNA molecules depends in the first instance on the individuals conducting the research. The Guidelines are designed to help the Principal Investigator determine the safeguards that should be implemented, and it is his or her responsibility to ensure that the purpose of the Guidelines is fulfilled. A number of the comments were devoted to the PI's role in laboratory safety and training.

Training. Many of the correspondents and several of the witnesses at the September 15 hearing recommended training programs for all laboratory personnel, including custodial personnel, the members of the Institutional Biosafety Committee, the Biological Safety Officer, and all relevant institutional officials. One commentator recommended that laboratory workers in P2 or higher facilities take and pass training courses or demonstrate equivalent competency before working directly with organisms containing recombinant DNA. Further, a centralized and uniform certification process for workers at the P3 or P4 level was advocated. It was urged that the Guidelines not be revised until there are uniform procedures for training certification of all biosafety officers and all recombinant DNA laboratories at the P2 or higher levels. Some suggested the Biological Safety Officer should be responsible for the certification process.

A number of commentators advised further that the Guidelines specify components of training for a program available to all potentially exposed workers. It was also recommended that the PI make available copies of approved protocols that describe potential biohazards and precautions, not only to the research personnel but also to the custodial staff. It was further suggested that NIH and OSHA should jointly sponsor technical and educational programs for IBC members and Biological Safety Officers.

I appreciate the concern regarding the quality and uniformity of training. As I stated in my Decision document (July 1978), NIH is responding to this by placing a high priority on the development of training standards and courses. For example, we are supporting, as noted previously, a working panel of the American Society for Microbiology that is considering standards for training in microbiological techniques for recombinant DNA research. When a report is submitted to NIH, it will be shared with institutions, IBCs, PIs, and BSOs. National certification of proficiency in any research technology is fraught with problems, especially in areas in which knowledge is increasing rapidly.

NIH is already sponsoring and developing courses on these standards of training. For example the University of Minnesota School of Public Health has developed and conducted a series of short courses on "Biohazard Containment and Control for Recombinant DNA Molecules" under the sponsorship of the National Cancer Institute's Office of Research Safety. The objective is to instruct laboratory workers on the principles of safety in the research laboratory and, particularly, on their application to the safe handling of recombinant DNA molecules. To date, six courses have been presented. A total of 221 participants from 97 institutions have attended. They have come from 7 government laboratories, 34 private or industrial laboratories, and 56 universities.

The Office of Research Safety, NCI, is also developing a training course for biosafety officers on practices and procedures for the control of biohazards in the research laboratory. The purpose is to equip biosafety officers with the basic knowledge and skills to carry out effectively the responsibilities specified in the NIH Guidelines. Detailed instruction on methods for evaluating, certifying, and monitoring physical-containment safeguards will be offered. Guidance will also be provided on how to organize, plan, develop, and conduct a comprehensive biosafety program.

NIH plans to further the biosafety training efforts of institutions by providing on-site consultation. The program will be designed to assist institutions and their IBCs, biosafety officers, and laboratory workers in effectively carrying out the requirements of the Guidelines. Biosafety professionals will be available to visit institutions and assist them in evaluating and improving their safety programs. These professionals will also be available to help solve specific problems in physical containment. A principal element of the program will be to promote good laboratory practice and to reinforce its importance.

Training of laboratory workers is a continuous process required under the Guidelines. One commentator expressed uncertainty as to who has the responsibility for seeing that personnel are trained in safety practices and

techniques. The DHEW Committee reviewed this matter, and on the basis of the review, the responsibilities have been clarified. The institution is responsible for ensuring appropriate training for IBC chairpersons and members, laboratory staff, and the BSO. The IBC chairperson will brief the IBC members and provide whatever information on training is required for them to fulfill their responsibilities. To the PI is delegated responsibility for training all the laboratory workers involved in the project.

Safety Practices. The PI is responsible for correcting work errors and conditions that may result in the release of recombinant DNA materials. Several commentators suggested that any accidental release of recombinant organisms, regardless of suspected pathogenicity, be reported to the proper health authorities. The Guidelines now require the institution to report to State and local health departments any significant research-related illness or accident that appears to be a hazard to the public health.

Another commentator suggested that the PI be required to halt ongoing research if any problems result in a failure to meet assigned containment requirements. It was suggested that the research be halted for 24 hours while a report is made to the IBC. The IBC would then certify in writing that the necessary repairs have been made. The Guidelines require reporting and correction of such problems by the investigator, but they do not specify a time limit except that reports must be made to NIH within 30 days on any significant problems with the Guidelines, on violations, and on all significant research-related accidents and illnesses. Nor do they require the IBC to document the reports. While these mandates are not necessary, the institution should consider setting such policies as deemed necessary. The Laboratory Safety Monograph and the Guidelines contain increased information on health surveillance to assist the PI in his responsibilities in this area.

Exemptions and Exceptions. Another commentator suggests that the PI receive IBC approval before petitioning the NIH for exemptions to the Guidelines or exceptions to the prohibitions. In light of the enhanced responsibilities of the local IBCs, it is appropriate for them to review proposals for exceptions to the prohibitions. Accordingly, the Guidelines now state that proposals to NIH must be submitted with the concurrence of the IBC.

Proposals for exemptions from the Guidelines deal with alterations in standards applied to all engaged in this research. Scientists may send those proposals directly to NIH for the considerations of the RAC with notice to the IBC. Note of exemptions granted will be sent to all IBCs. Experiments that are exceptions to the prohibitions require approval at the national level, after which they must be reviewed and approved by the IBC. An MUA must then be approved by NIH before the experiment may be initiated.

MUAs. Several commenters suggested that the Guidelines be clarified with respect to the types of experiments that may not be started prior to NIH approval. As noted previously, the Administrative Practices Supplement is responsive to the suggestion, and more guidance is given in the section of the Guidelines on "Institutions" (IV-D-1) to clarify the preparation and submission of MUAs for new and modified experiments.

Publication. The Guidelines recommend that published research articles specify the containment procedures used. A commentator advocates that this be required. The issue has been raised before, and it remains our view that NIH neither can nor should control what must be included in scientific publications.

RESPONSIBILITIES OF NIH (GENERAL)

Due Process Considerations

A number of commentators spoke on the issue of public participation, including how best to inform the public and ensure public access to NIH proceedings. A number of commentators and witnesses at the September 15 hearing focused on the provisions calling for "appropriate notice and opportunity for public comment." Several suggested that those provisions be described in greater detail in the Guidelines. Other commentators urged that labor and environmental representatives, consumer advocacy groups, public health officials, and government agencies with potential regulatory responsibility have full access to decision-making.

Some commentators called for clarification of procedures for certifying host-vector systems. Others asked that the standards and procedures for future Guideline revisions be explicitly stated. Another wanted procedures that clearly set forth public notice and comment in advance of RAC decisions. And another believed the proposed Guidelines "exacerbate the problems of self-regulation" and urged that "HEW supervise the administration and enforcement of the Guidelines."

One commentator suggested a procedural mechanism for minor or partial revisions. He advised that RAC recommendations be published in the FEDERAL REGISTER for comment, and that the comments be taken into account by the RAC before it forwards final recommendations to the Director. Thus, NIH in these cases would act in the light of advice reflecting public views.

Another commentator suggested that each time NIH receives an application for an exception to a prohibited experiment, notice be published in the FEDERAL REGISTER, and that after a public comment period, final notice of agency action should also be published there.

NIH Procedures. The NIH Guidelines of 1976 provided little or no discretion in their administration or revision. As a result, many recommendations by the RAC could not be accepted because of NIH's lack of authority under those Guidelines to approve them. The revision proposed by the RAC in September 1977 attempted to correct this inflexibility by providing for discretion under specified conditions, with procedures set forth to ensure opportunity for public notice and comment. However, the standards and procedures for exercise of discretionary authority in the proposed revision, as many of the commentators pointed out, needed greater definition and clarity.

The commentators' procedural recommendations provided a focus for the DHEW Committee in its intensive review of these issues in the proposed revisions. Other comments from the scientific community, from many witnesses at the public hearing, and from a DHEW meeting with environmental interest groups augmented the efforts to define avenues for appropriate utilization of NIH authorities. On the basis of the comments made in correspondence and at the September 15 hearing, part IV has been substantially revised to provide for public access and participation in NIH activities under the Guidelines. It clearly sets forth the procedures that will govern the exercise of NIH authority.

First, there is a group of major actions for which the NIH Recombinant DNA Advisory Committee (RAC) will advise the Director after an opportunity for public and Federal agency comment. These actions include lowering or assignment of containment levels where the Director judges the action to be major; certification of new host-vector systems; exceptions to the prohibitions; modification of a list of recombinant DNA sources (microorganisms) to be exempt from the Guidelines and other changes in the Guidelines.

For these major actions the following procedures apply. The Director must seek the advice of the RAC and provide an opportunity for public and Federal agency comment. Specifically, the agenda of the RAC meeting citing the major actions will be published in the FEDERAL REGISTER at least 30 days before the meeting, and the Director will simultaneously publish the pro-

posed actions in the FEDERAL REGISTER for comment. In addition, the Director's proposed decision, at his discretion, may be published in the FEDERAL REGISTER for 30 days of comment before final action is taken. The Director's final decision, along with response to the comments, will be published in the FEDERAL REGISTER and the *Recombinant DNA Technical Bulletin*. The RAC and IBC chairpersons will be notified of this decision.

There is a group of lesser actions for which the RAC will advise the Director after a meeting announced as described above. These actions include all interpretations of determinations referred by ORDA, changes and assignment of containment levels, approval of large-scale experiments for rigorously characterized recombinant DNA where the absence of harmful genes has been established, and designation of certain class 2 agents as class 1 for purposes of the Guidelines. The Director's decision will be transmitted to the RAC and IBC chairpersons and published in the *Recombinant DNA Technical Bulletin*.

And finally, there is a group of administrative and scientific functions in the Office of the Director that may be delegated to the Office of Recombinant DNA Activities (ORDA), involving implementation of the Guidelines and their interpretation. Again, decisions by the Director in these matters will be published in the *Recombinant DNA Technical Bulletin*, and notice will be given to the RAC and IBC.

There was considerable Committee discussion on the standards to guide administrative discretion. It was agreed that the Guidelines should set forth a general standard. Accordingly, they now charge the Director to "with each proposed action, through appropriate analysis and consultation, to determine that it complies with the Guidelines and presents no significant risk to health or the environment." For a discussion of NIH efforts in risk assessment, see part III of this document and the Environmental Impact Assessment (Appendix I).

The Guidelines now reflect these roles and relationships in detail and identify all of the responsibilities in cross-reference on the other sections of the Guidelines and to the Administrative Practices Supplement. As indicated above, opportunities are afforded for public access and participation, with formal procedural requirements based on the significance of the discretionary authority. In light of these procedures, hearings by the Director's Advisory Committee may be unnecessary; but if circumstances warrant, the committee can play an oversight role as it has done in the past.

Recombinant Advisory Committee Membership. The correspondents and witnesses at the September 15 hearing who commented on process considerations also expressed opinions on membership of the Recombinant DNA Advisory Committee (RAC). A number of recommendations were made concerning representation. Some witnesses at the September 15 hearing urged that representatives from the regulatory agencies, such as the Environmental Protection Agency, the Food and Drug Administration, and the Occupational Safety and Health Administration, have full voting membership on the RAC. It was also suggested that a representative from the Council on Environmental Quality serve on the committee. The view was expressed that the representation of these agencies on the Federal Interagency Advisory Committee on Recombinant DNA Research could not substitute for their full participation on the RAC. And it was suggested that representatives from the regulatory agencies constitute a subcommittee of the RAC for purposes of considering all future modifications of part IV.

Some Federal agency commentators suggested that representatives from research agencies such as the National Science Foundation, the Department of Agriculture, and the Veterans Administration serve on the RAC, and perhaps be permitted to consider exceptions to the prohibitions in the Guidelines.

Several commentators recommended that representatives from unions and public interest groups serve on the committee. Quotas for membership were also suggested for public interest groups, unions, and nonprofessional laboratory workers. Public interest members might also be permitted to consider exemptions and exceptions to the prohibitions.

There were a number of recommendations concerning professional and scientific expertise. One commentator advocated representation from "knowledgeable specialists in environmental processes and effects on ecosystems and their biota." Other recommended that the committee include scientists from Federal research agencies, scientists critical of the guidelines, and experts in epidemiology, medical microbiology, and clinical infectious disease research. And finally, it was suggested that RAC be advisory to the Department rather than to NIH.

Many of these concerns were raised at the December 1977 meeting of the Director's Advisory Committee (DAC) by witnesses commenting on the revised Guidelines as proposed by the RAC. As I stated in addressing those concerns in my July 28, Decision, I am acutely aware of the need for broad representation on the RAC, and this was considered in the selection of new members.

To ensure fairness, however, nominations for openings on the RAC are publicly and widely solicited. In July 1978 a notice was filed in the FEDERAL REGISTER requesting public recommendations for RAC membership. All nominations are considered in selecting members of the committee. This open nomination process will be repeated annually, and thus NIH will not be the only source of RAC nominations. Further, nominations are being solicited from all agencies represented on the Federal Interagency Advisory Committee.

There was considerable discussion by the DHEW Committee about the membership of the RAC. The present RAC has 16 members, 2 of whom are lay persons. The DHEW Committee agreed that the composition should reflect the requirements set for the IBCs at the local level. Thus, it is required that at least 20 percent of the RAC members shall be persons knowledgeable about such matters as applicable law, standards of professional conduct and practice, public and occupational health, and environmental safety. In addition, it is recommended that one member be a "nondoctoral" person from a laboratory technical staff.

It was also agreed that the scientific representation on the committee should be broadly based to include persons knowledgeable in recombinant DNA technology and biological safety, but also with expertise in the broader disciplines of biology and medicine—i.e., microbiology, molecular biology, botany, ecology, virology, genetics, infectious disease, plant pathology, and epidemiology.

In view of the expanding role and responsibilities of the RAC, it was though appropriate to augment the expertise and representation. Under a new chapter, the RAC will be expanded to 20 members.

In addition, all Federal agencies represented on the Federal Interagency Advisory Committee will have nonvoting members on the RAC. (At present, some research agencies already have liaison members, such as the National Science Foundation and the Department of Agriculture.) These representatives will be nonvoting because of the large number of Federal agencies involved, but they will be participating members encouraged and enabled to present their agencies' concerns on scientific and other issues.

All members of the RAC may participate on the several subcommittees of the full committee. Thus, there is clearly no need to mandate the nature, structure, or function of subcommittees created by the chairperson in consultation with committee members. Finally, the RAC is advisory to the Sec-

retary of HEW and the Assistant Secretary for Health, as well as to the Director, NIH.

Pending the expansion and restructuring of the RAC, no changes will be made in these Guidelines and no decisions will be made requiring the RAC's prior review and advice.

Federal Interagency Advisory Committee and Recombinant DNA Research. A meeting of the Federal Interagency Advisory Committee and Recombinant DNA Research was held on October 12, 1978, to consider agency comments on the proposed revised Guidelines and proposed roles for the committee. Several agency representatives noted that under the discretion granted in the Guidelines, cognizance should be taken of Federal agency roles. Enhancement of the roles for Federal agencies other than NIH was discussed with the committee. This included the proposal of nonvoting membership on the RAC, as noted above, and nominations from the agencies for potential voting members. As defined under the new procedures promulgated in part IV, all Federal agencies through their members will have an opportunity to participate in the RAC proceedings and may file written comments concerning RAC activities. Interagency Advisory Committee members will receive RAC agendas and FEDERAL REGISTER notices.

In additions to participating in the proceedings of the RAC, all agencies represented on the Federal Interagency Advisory Committee are now afforded an opportunity to request a meeting of that committee to consider RAC actions in light of their concerns. Some RAC actions, like a recommendation to release recombinant organisms into the environment, will undoubtedly necessitate a meeting of the Interagency Advisory Committee to provide information and seek concensus. Periodic meetings of this committee will also continue to be held for evaluation of recombinant technologies and their regulation under the Guidelines. (For reference, a list of the agencies represented on the Interagency Advisory Committee is presented in Appendix II.)

Scientific Counselors for ORDA

ORDA will provide consultation to Federal agencies regarding the Guidelines, and a board of scientific counselors from all Federal agencies that support or conduct recombinant DNA work will advise ORDA on the activities of the Office of the Director, ORDA, and the RAC. A key task for the board will be to ensure a common registry of all federally funded recombinant DNA research.

The DHEW Committee expressed the wish that Federal cooperation continue, and stronly endorsed the new responsibilities of the Federal agencies under the revised Guidelines.

RESPONSIBILITIES OF NIH (SPECIFIC)

Office of the Director

The principal issues here relate to the standards and procedures for governing the discretion of the NIH Director under the Guidelines. All of the responsibilities that the Guidelines assign to the Director are now grouped under "general responsibilities" (for promulgating rules and overseeing implementation of the Guidelines) and "specific responsibilities," which include the opportunity for public and Federal agency comments. This new organization clearly delineates the responsibilities and the procedures and standards to govern the exercise of discretion based on the advice of the RAC and ORDA.

The DHEW Committee discussed the need for periodic review and assessment of NIH's experience in conducting and supporting recombinant DNA research. Accordingly, it was agreed that appropriate language should be inserted in the Guidelines that the Director, at the end of 36 months from their implementation, will report on the Guidelines and NIH experience under them in consultation with the RAC and the Federal Interagency Committee. He will solicit public comment on the draft before transmitting the final report with response to comments to the Assistant Secretary for Health and the Secretary, HEW.

In addition, the Director is now responsible for supporting training programs in laboratory safety for IBC members, Biological Safety Officers, Principal Investigators, and laboratory staff.

Recombinant Advisory Committee

A major concern of the witnesses at the September 15 hearing, and of the commentators on the proposed revised Guidelines, was related to the composition of the RAC, as discussed above. The new procedures clearly guide the discretion of the committee and provide for full public and Federal agency participation. The responsibilities of the RAC have been enhanced, with full access to the public and the Federal agencies. As I stated in my Decision of July 1978 accompanying the proposed Guidelines, the task for all RAC members has been enormous and their work and spirit of cooperation have been exemplary. I look forward to continued cooperation with Dr. Jane Setlow, Chairman, and all of the committee members. Their assistance is vital to the integrity of this research under the Guidelines.

Office of Recombinant DNA Activities

The majority of comments concerning ORDA focused on the office's oversight responsibility. The issues concerning delegation of authority to the IBC's and the role of ORDA in registering not only recombinant DNA activities but other data relating to health surveillance have been discussed in the previous section on local institutions.

There were several comments concerning the need for increased staffing for ORDA to meet the new responsibilities under the Guidelines. Additional staff has been provided, and there will be need for more in light of the new responsibilities of the Recombinant Advisory Committee to solicit public and Federal agencies' comments.

As noted previously in the section on the Interagency Committee, a board of scientific counselors from the other Federal agencies that conduct or support recombinant DNA research will be established as advisory to ORDA. This board is created in response to suggestions from Federal agencies for some mechanism to ensure uniformity in interpretations and determinations made under the Guidelines where discretion is granted. An early task of the board will be to assist in creating and maintaining a registry for all recombinant DNA activities funded by the Federal Government. The board will also assist ORDA's Director in forwarding to the RAC all requests from other Federal research agencies for action on such matters as certification of new host-vector systems. We are, in fact, trying to ensure a capability for uniform interpretation and implementation of the Guidelines throughout the Federal sector.

Another commentator urged that a time-frame be set for implementing the new standards and procedures. This request is a most important one. In anticipation of the release of the Guidelines, procedures have been drawn up for meeting the new requirements. Dr. William Gartland, Director of ORDA, has sent a letter to all institutions, IBC chairmen, and Principal Investigators, specifying the measures to be taken within the next three months to implement the new Guidelines effectively.

Registration. Here the principal comments came from the Federal agencies and private industry. The proposed revised Guidelines require the institutions that receive NIH funds for recombinant DNA research to register all recombinant DNA projects, irrespective of the source of funding. Representatives from Federal research agencies pointed out that institutions should not be required to register with NIH if they are already registering with the Federal agency that supports the work. Accordingly,

the Guidelines now specify that an institution need not register with NIH its projects funded by another Federal agency when that agency maintains a registry and provides the NIH with essential information. The institution will register projects directly with NIH if the supporting Federal agency does not choose to maintain its own registry.

At a meeting held with the DHEW Committee, representatives of the Pharmaceutical Manufacturers Association urged greater protection for proprietary and patent information under the Guidelines. The proposed revised Guidelines offered a system of voluntary registration and certification for the private sector which was not available under the 1976 Guidelines. In addition, a representative from the Commerce Department also urged expansion of the Guidelines to protect proprietary and patent information. On the other hand, environmental interest groups have expressed concern that there be maximum disclosure of information. Because of the complexity of the issue, and the general perception that NIH does not have the powers to completely protect proprietary rights and trade secrets, this aspect of the Guidelines will be handled separately after their issuance. The Food and Drug Administration is now considering issuing regulations that would require drug companies to comply with the NIH Guidelines.

Compliance. Several of the commentators and witnesses at the September 15 hearing recommended stronger language in the Guidelines concerning compliance with the Guideline provisions. The proposed revision stated that noncompliance may result in suspension, limitation, or termination of financial assistance. Several commentators urged that the language be made mandatory. Others suggested that possible violations be ranked, with definite penalties set in each case, including criminal penalties. Still others urged invocation of Section 361 of the PHS Act to ensure compliance through regulation.

Many of these issues were raised at the December hearing of the Director's Advisory Committee and in correspondence on the Guidelines as proposed by the RAC. In response to the suggestions, a section on compliance was included in the proposed revision. However, as I noted in my Decision accompanying that publication, NIH has no authority to impose fines in the absence of new legislation. I also noted that appropriate HEW procedures will be followed should suspension or termination of a grant be necessary. In light of the lack of statutory authority, penalties for negligence and criminal penalties should not be specified. It has been suggested that NIH might seek reimbursement for any funds expended upon activities not conducted in accordance with contractual assurances. This recommendation differs from current HEW grant policy and will require much more consideration.

On the basis of DHEW Committee discussion, a new provision will allow NIH to require prior approval of any and all recombinant DNA research projects if the institution fails to compy with the Guidelines.

Invocation of Section 361 of the Public Health Act has been carefully considered by the Interagency Committee and the Department over the past two years. The most recent expression of interest in this authority was in a letter six Senators requesting Secretary Califano to consider invoking Section 361 to regulate recombinant DNA research. The letter and the Secretary's response are included in Appendix III to this Decision. Briefly, the Secretary said that the Department does not intend to evoke existing statutory authorities to regulate recombinant DNA activities at this time. He went on to quote the Interagency Committee's report of March 15, 1977, dealing with elements for legislation, including the determination that Section 361 would require a reasonable basis for concluding that recombinant DNA research may cause human disease. Such a conclusion is tenuous at best and would at present be an inappropriate basis for invoking the regulation. The Secretary, however, noted in his letter that if the Department had to act speedily, Section 361 is available and would be used. In the Secretary's view, only legislation would justify establishing regulations.

V. Footnotes and References

In reply to correspondents' suggestions and NIH review, minor changes have been made in Footnotes 3 and 5; and five new footnotes—2A, 19A, 33A, 33B, and 37A—have been added.

A correspondent recommended that text be added to Footnote 2 to discuss the basis for allowing cloning of genetic information from *Vesicular stomatitis* virus and moderate-risk oncogenic viruses. Since Footnote 2 already refers the reader to the July 28, 1978, Decision document, where this is discussed in detail, no further discussion in Footnote 2 seems necessary.

Appendix A

(Director's Decision concerning Appendix A of the Guidelines)

There were many comments concerning the list of exchangers in Appendix A to be exempted from the Guidelines under Exemption I-E-4.

Some correspondents recommended additions to the list, including *Caulobacter crescentus, Agrobacterium, Proteus,* and *Xanthomonas.*

On the other hand, some correspondents felt that there was insufficient documentation for the entries on the list and that the list should be by species, not genus.

One correspondent recommended citing Bergey's *Manual of Determinative Bacteriology.* Another wrote, "It is also questionable why one should list *Escherichia coli* exchangers and not others in nature such as the organisms that exchange with *Bacillus subtilis,* with *Haemophilus influenzae,* with *Neisseria gonorrhoeae,* etc."

In response to the many comments received, the list of organisms to be exempt from the Guidelines under Exemption I-E-4 has been carefully reconsidered. The discussion below attempts to make more explicit the considerations used in constructing this list. In addition, the criteria for inclusion on the list have been tightened, reducing the list considerably and thus exempting fewer experiments from the Guidelines. References supporting the entries to the list are given below (refs. 1-22). The final list (Appendix A) closely resembles the "first list" described in Appendix D to the July 28, 1978, Environmental Impact Assessment.

It should be emphasized that the evolution of this list will continue as more experiments are done and as we gain more knowledge in this rapidly advancing field. In addition, other organisms recommended by some of the commentators (*Bacillus* or *Haemophilus* species, for instance) are currently being considered by the RAC for future inclusion under this exemption.

As noted in Appendix D to the July 23, 1978, Environmental Impact Assessment: "The natural transfer of genes between bacteria occurs by transduction (bacterial virus-mediated), transformation (uptake of isolated DNA by a bacterial cell), or conjugation (plasmid-mediated transfer of genes between bacteria requiring cell-to-cell contact). A reasonable generalization is that virtually all closely related species of bacteria can exchange genes by transduction and transformation, the former limited by the relatively narrow host-range of transducing bacteriophage and the latter by the requirement, in the case of chromosomal DNA, for homology of DNA in most recombination events. Conjugal mating with exchange of DNA can occur between virtually all Gram-negative bacteria, including naturally occurring soil and intestinal species, when mediated by a plasmid of broad host-range (for example, the Inc P-1 group plasmids). Recently, conjugal mating has also been shown to occur between strains of certain species of *Streptococcus,* a Gram-positive organism (for example, *Streptococcus faecalis*). To date, however, conjugal mating has not been demonstrated between Gram-negative and Gram-positive bacteria.

"The relatedness of different microbial species can be estimated by determining the extent of DNA homology between them or by studying the properties of different microorganisms in genetic crosses. As a general rule, organisms that show considerable homology of their nucleotide sequences under a standard set of experimental conditions have the capacity to mutually integrate chromosomal genes. For example, in the case of the *Enterobacteriaceae* family of bacteria (includes *Escherichia coli* K-12), there is both extensive DNA-DNA homology (1) and chromosomal gene exchange (2) with a reasonable correlation between the degree of DNA-DNA homology and the capacity to mutually integrate chromosomal genes.

"Genetic relatedness, as indicated by a high level of DNA-DNA homology between different microorganisms, is not, however,

an absolute requirement for the exchange of chromosomal genes between bacteria. In fact chromosomal gene transfer among diverse members of the Gram-negative group of bacteria has been demonstrated where the microorganisms involved show little or no DNA-DNA homology. In these cases the exchange of chromosomal genes is promoted by a broad-host-range plasmid of the Inc P-1 incompatibility type. These plasmids mobilize the chromosomes of a wide variety of Gram-negative bacteria, incorporate segments of these chromosomes, and are capable of establishing themselves along with covalently linked chromosomal genes in a wide range of Gram-negative bacteria. (3)"

In evaluating a pair of organisms for inclusion as nonnovel exchangers, we are making an estimate of the probability that the combination of genes might have occurred naturally. If the combination is not a new one, then there should be no special hazard in creating such an organism by recombinant DNA technology. Thus we can exempt this combination from the Guidelines.

Any conclusion about exchange between organisms involves some extrapolation from the experimental data available. We have tried, in the discussion below, to make explicit these extrapolations and the scientific bases for making them. For this purpose, the types of criteria which might be taken into account in preparing a list of exchangers are divided into four categories. The first two were those used in constructing Appendix A in these final revised guidelines. The first three were used in constructing the version of Appendix A which appeared in the July 28, 1978, proposed revised guidelines. All four were used in constructing a list approved by the RAC and described as the "third list" in Appendix D to the July 28, 1978, Environmental Impact Assessment.

1. *Organisms which exchange chromosomal genetic information which becomes stably integrated into the host chromosome.* This, the most stringent criterion for exchange, requires significant homology between recombining segments. Organisms which meet these criteria will therefore be closely related by DNA homology measurements (Ref. 1, 2). In addition, more than one mechanism of genetic exchange may be found (i.e., transduction and plasmid mobilization), and transfer of many different markers may be demonstrated. The major extrapolation involved in this category is the extension of data from one strain to others in the same species or genus. In the Appendix A list, most of the entries are listed as genera (*Shigella, Salmonella*, etc.), while the *Pseudomonas aeruginosa* species is listed. One can generalize from species to genus when there is evidence that all members of the genus behave similarly, and show extensive DNA homology. In addition, in some cases, exchange has been demonstrated in many species of the genus. The DNA homology test is convincing for *Shigella*, but not for *Pseudomonas*.

2. *Organisms which exchange chromosomal information that is not necessarily integrated into the chromosome of the recipient (for instance, transfer via F' or R).* This sort of exchange can occur in the absence of extensive DNA homology between the organisms, and requires only that the plasmid and its chromosomal genes be maintained in the recipient organism.

Although two organisms meeting these criteria might not be closely related, this type of exchange is probably the best model of a recombinant DNA experiment. In both cases, relatively small amounts of genetic information are transferred, usually in plasmid form, to an otherwise "foreign" genetic background. Therefore, it seems reasonable to accept evidence of such exchange as grounds for exemption.

Criteria 3 and 4 deal specifically with Inc P-I plasmids, but the principles can be extended to other exchange mechanisms.

3. *Organisms which show evidence of a plausible mechanism for exchange (e.g., R' formation or evidence of mobilization of chromosomal genes by an Inc P-1 plasmid.)* In this case, the plasmid itself has been shown to move from organism to organism. It has been shown to pick up chromosomal genes, but the transfer of these chromosomal genes in interspecies matings has not necessarily been demonstrated.

To endorse these criteria, we must extrapolate from the transfer within the species to more distantly related organisms. For such an extrapolation, one must assume that no barriers will exist for R' transfer that do not exist for transfer of the plasmid itself. In many tested cases, this is clearly true: transfer of chromosomal genes incorporated into an R factor is comparable in frequency to transfer of the plasmid itself, and the R' can be moved to a broad range of organisms (4). However, this may not be universally true (5).

4. *Organisms which can receive or donate broad host range plasmids.* Since these plasmids are known, in many cases, to mobilize the chromosome and transfer chromosomal genes, such transfer might be expected for any organism that receives or donates the plasmid. This extrapolation assumes that (i) chromosomal pickup is always able to occur with these plasmids and (ii) transfer of chromosomal genes to other species will occur (this latter case is the same at that analyzed under criterion 3).

Analysis of the basis for the first extrapolation would include consideration of the numerous cases where such mobilization and transfer can be detected (see, for instance, ref. 5-10) and those few where it cannot (11).

It is my decision that the data supporting the use of criteria 3 and 4, while suggestive, are not yet compelling enough to warrant exemption from the Guidelines for recombinant DNA experiments. As more data are accumulated, this conclusion will be carefully reconsidered.

The Issue of Two-Way Exchange

The organisms listed in appendix A fit the first two criteria described above—i.e., in all cases, there is direct evidence of chromosomal exchange between two species on the list, and many show extensive DNA homology as well. In addition, for all the organisms on this list, exchange can be demonstrated in two directions. Further, if organisms A and B both exchange genetic information (both donate and receive) with a third organism—*E. coli* K-12, for instance—then *E. coli* K-12 can act as a path for the DNA of organism A to reach B, and *vice versa*. Thus, the requirement for two-way exchange allows us to exempt recombinants made between A and B. Therefore, we have exempted "any recombinant DNA molecules that are (1) composed entirely of DNA segments from one or more of the organisms listed below and (2) to be propagated in any of the organisms listed below."

It would make sense, of course, to have one-way lists as well, where cloning exempt from the Guidelines would only be allowed in the recipient. The creation of such lists will be considered by the RAC.

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APPENDIX B

(Director's Decision concerning Appendix B of the Guidelines)

Three correspondents correctly point out that since the publication in 1974 of the "CDC Classification of Etiologic Agents on the Basis of Hazard" (which is repeated verbatim as Appendix B to the Guidelines), *Actinomycetes* have been reclassified. Formerly considered to be fungal agents, they are now considered bacterial agents. An explanatory footnote has been added to the table.

APPENDIX I—ENVIRONMENTAL IMPACT ASSESSMENT

ENVIRONMENTAL IMPACT OF THE FINAL GUIDELINES

An *Environmental Impact Assessment of the NIH-Proposed Revised Guidelines* (EIA) was published with the Guidelines in the FEDERAL REGISTER of July 28, 1978. The assessment was based on an intensive analysis of the Guidelines then in effect, the Guidelines as proposed by the Recombinant DNA Advisory Committee in September 1977, and the Guidelines as proposed by NIH in July 1978. The conclusion of the assessment was that there would be no adverse impact of the NIH-proposed changes upon the environment.

The issues raised by the commentators in correspondence and by the witnesses of the September 15 hearing on the NIH-proposed revised Guidelines are reviewed in detail in the accompanying Decision document. It is the conclusion, based on that review of the alternatives proposed in July 1978 and the decisions reflected in the final Guidelines, that there will be no adverse impact of the Federal actions upon the environment. Indeed, in the extensive revision of part IV, these final Guidelines enhance public participation and accessibility at the national and local levels, with increased emphasis on health surveillance and safety training. The final Guidelines provide an even stronger framework to ensure that no significant risk is presented to the public health or the environment.

Consideration now follows of certain issues relating to the EIA of July 28, 1978, which were raised in correspondence and by witnesses at the September 15 hearing.

NEPA Considerations

A witness at the September 15 hearing cited the EIA as being inadequate and held that a full Environmental Impact Statement (EIS) should be prepared. The witness stated that an EIS is clearly required by the law. In addition, the witness found the EIA inadequate in its analysis of the revisions in such areas as exemptions and the use of *E. Coli.* K-12 and other host-vector systems.

In our view, the EIA prepared by NIH on the proposed revisions to the NIH Guidelines fully satisfies the requirements of the National Environmental Policy Act of 1969 (NEPA).

The current Guidelines on Recombinant DNA Research were issued on June 23, 1976, and published in the FEDERAL REGISTER on July 7, 1976 (41 F.R. 27902). They were developed by NIH after opportunity for public comment and an open meeting at which members of the public were invited to testify (41 F.R. 2105).

In the Decision of the Director, NIH, which accompanied the 1976 Guidelines, it was indicated that NIH would prepare a draft EIS on the Guidelines in order to give the public further opportunity to comment. The draft EIS was published in the FEDERAL REGISTER on September 9, 1976, with a preamble soliciting public comment (41 F.R. 38426). After the close of the comment period, a final EIS was prepared, taking into account the comments received and scientific developments up to that time. The EIS actually became final on November 28, 1977, when notice of its receipt was published in the FEDERAL REGISTER by the Council on Environmental Quality (42 F.R. 60588).

During this period, scientific evidence has been accumulating that the risks presented by recombinant DNA research, which has always been purely speculative, were indeed remote. As a result, it became apparent that the restrictions in the Guidelines were more stringent than necessary and that the Guidelines needed to be revised. The process of revision was first undertaken by NIH's Recombinant DNA Advisory Committee (RAC), which referred a proposal for revision to the Director, NIH, in September 1977. On September 27, 1977, the Director published the RAC's proposal in the FEDERAL REGISTER for public comment (42 F.R. 49596). At the same time, and in a subsequent FEDERAL REGISTER notice (42 F.R. 59918), the Director announced a two-day meeting to secure public testimony on the RAC proposal. This meeting was held on December 15-16, 1977, and witnesses appeared from environmental groups, the scientific community, and industry.

Based on the comments received and the testimony at the December meeting, the Director developed an NIH-proposed revision of the Guidelines (referred to herein as the PRG), relying in part on the RAC proposal. The PRG was issued by the Director, as a proposal, with the approval of the Secretary, on July 19, 1978, and published in the FEDERAL REGISTER on July 28, 1978 (43 FR 33042), the preamble to the PRG requested public comment, announced that a further hearing on the PRG would be conducted on September 15, 1978, before an HEW panel chaired by the General Counsel, and indicated that final action on the PRG would be taken after the panel had reviewed both the written comments and those provided at the hearing.*

When the PRG was published on July 28, it was accompanied by a detailed EIA, which included a discussion of the risks and benefits of recombinant DNA research and an analysis of the current Guidelines, of alternatives to the Guidelines, and of NIH's PRG. In addition to an overall assessment of the environmental impact of the PRG, sepaate environmental impact analyses were made of each section. The conclusions reached were summarized at the beginning of the EIA as follows:

> As can best be determined from all evidence compiled to date and analyzed in numerous scientific and public forums, there will be no adverse environmental impact from recombinant DNA research conducted under the Director's proposed revisions. The Environmental Impact Statement on NIH Guidelines for Research Involving Recombinant DNA Molecules, issued in October 1977, predicted that the environmental impact of research conducted under the 1976 NIH Guidelines would be the continued protection of the laboratory worker, the general public, and the environment from conjectural hazards. So far, this prediction has been confirmed: We know of no scientists conducting recombinant DNA research in the United States or other countries who are not following the NIH or comparable guidelines, and no untoward effect of the research has been reported. Meanwhile, new scientific evidence as well as extensive experience in operating under the NIH Guidelines indicate that revisions are in order. The predictable effect of continued use of recombinant DNA techniques under the Director's proposed revisions would be a greater realization of the benefits of this valuable tool without compromise of safety. (43 FR 33096).

The EIA prepared by NIH on the PRG discusses in detail scientific developments regarding recombinant DNA research. It justifies the changes proposed by NIH, explains why some RAC and public proposals were not ac-

* More than 30 persons from environmental groups and the scientific community testified at the September 15 hearing.

cepted, and assesses at some length the anticipated environmental effects of the changes NIH proposed to make.

In my view the EIA represents a conscientious, thoughtful, and thorough effort to carry out our responsibilities under NEPA. As one correspondent noted, the assessment is a "thorough and fully documented analysis • • • that describes the technical aspects of this research and its conjectural risks and benefits." The EIA took a "hard look" at the current Guidelines, the various alternatives, and the environmental implications of the proposed changes. By soliciting public comment and conducting a public hearing, relevant areas of environmental concern were identified. I believe that a convincing case is made in the EIA that the proposed changes would have no significant environmental impact.

My Decision accompanying these final Guidelines reviews at some length exemptions from the Guidelines in light of the comments made by correspondents and witnesses. And indeed, a lengthy analysis of the list of exempt organisms in Appendix A documents the prudence and caution in which NIH is proceeding. On the basis of comments, the list has been modified and the scope of experiments restricted.

It was also asserted by witnesses that the filing of an EIS would provide for public input in the Government's decisions affecting the environment. In my view, NIH's overall response to the issues raised by recombinant DNA research has been to ensure a full public hearing of all issues. When these issues first arose, NIH conducted public hearings, solicited public comment, developed Guidelines, and published an EIS, which ultimately received judicial approval.

Since that time scientific evidence has shown that the initial concerns about the hazards of this research may have been exaggerated. Accordingly, we proposed to relax some aspects of the Guidelines. In doing so, we again conducted hearings and solicited public comment. And the NIH-proposed revised Guidelines were published for comment, followed by a hearing under the aegis of a DHEW committee chaired by Peter Libassi, the DHEW General Counsel. In addition, all of the proceedings and all documents have been published in an ongoing series of volumes that document the basis for NIH policies. The documents contain relevant proceedings of the executive, legislative, and judicial branches. A fourth volume will be published in January containing the transcript of the September 15, 1978, hearing, all correspondence received by NIH commenting on the proposed Guidelines of July 28, 1978, and all other relevant documents.

RISK ASSESSMENT

Several witnesses raised issues concerning the concepts of risk and safety as outlined in the Environmental Impact Assessment (EIA). One witness emphasized the concept of risk as "a relatively objective measurement of hazards" and safety as "a subjective expression of the level of risk which is acceptable to a population." He believes the NIH Guidelines and Assessment confuse these two concepts. The Guidelines, in his view, do not provide adequate institutional mechanisms to ensure that the value issues involved in safety are thoroughly aired by the general public. Thus, because safety is "value-laden, subjective, and in a sense, political," the Guidelines must reflect these values by ensuring adequate mechanisms for determining safety standards and their implementation.

The October 1977 EIS on the original NIH Guidelines and the July 1978 EIA on the proposed revisions address in great detail occupational and environmental health and safety concerns. As noted in the EIA (FEDERAL REGISTER, p. 33131, middle column), several changes are proposed in the revised Guidelines "in the implementation, review, and monitoring of recombinant DNA activities at the local and national levels, to insure appropriate safety practices and procedures that would minimize any significant environmental impact."

These modifications focus on a restructuring of roles and responsibilities. The applicability of the Guidelines has been extended to all recombinant DNA research at institutions that receive any recombinant DNA research support from NIH. Biosafety committees have been given broader responsibilities. At the request of several commentators, Appendix D to the original Guidelines has been revised and updated as *Laboratory Safety Monograph—A Supplement to the NIH Guidelines*. The monograph is a compendium of useful safety information, including instructions on emergency procedures, laboratory techniques for biohazard control, and decontamination and disposal methods. It provides much detail on the responsibilities of the local institution for safety practices and procedures. The impact of these actions and the restructuring of part IV of the Guidelines will be the promotion of safer conduct of this research, affording a greater measure of protection to the environment, with emphasis on occupational health and safety.

Several commentators also urged NIH to initiate and fund a comprehensive risk-assessment program to provide a scientific basis for defining appropriate containment requirements for recombinant DNA experiments. The DHEW Committee reviewed NIH efforts in this regard. It was noted that recombinant DNA research experiments provide a great deal of information on risks. In addition, NIH is supporting a number of studies in risk assessment. The participants at the Falmouth Conference* recommend studies in six areas, and NIH is following up on those recommendations.

The Rowe-Martin polyoma experiments are discussed in the Decision Document. In addition, intramural NIH scientists are collaborating with scientists from other institutions in testing the virulence in mice of *E. coli* K-12 containing "shotgun clones" of recombinant DNA derived from other species.

A number of contractors of the National Institute of Allergy and Infectious Diseases are testing the biological containment capabilities of various derivatives of *E. coli* K-12. Some are testing the survival and capacity of plasmid and phage vectors to be transmitted to secondary bacterial hosts in the gastrointestinal tract of man and mouse. Others are assessing these parameters in model sewage treatment systems and in situations simulating accidental spills and other types of accidental release of the organisms for experimental procedures.

In addition, investigators proposing systems to be certified by NIH as HV1 or HV2 must perform certain specified tests on these systems relevant to their survival and transmission properties. It is also anticipated that if investigators seek exceptions to the prohibitions for specified clones, NIH will request substantial risk-assessment experiments to be performed to evaluate claims of safety.

Another commentator noted that Dr. Sidney Brenner of the Medical Research Council's Laboratory for Molecular Biology in Cambridge, England, had stated that he believed the whole method of risk-assessment up to now is "fragmentary" and that what is needed is a "more systematic approach," which he was trying to take. Dr. Brenner, when asked for more information on his studies, explained that the method of risk-assessment he referred to is not a new experimental approach but a new analytical approach. Dr. Brenner's work will be followed closely for any new information that sheds light on potential risks or safety of experiments under the Guidelines.

SOCIAL ETHICS

A witness at the September 15th hearing noted that "the steps taken to insure containment are of great immediate importance and the present guidelines should be continued." But

*See Journal of Infectious Diseases, 137:704-708, May 1978

he stated that "ultimately the discussion, kinds of facility and guidelines are simply irrelevant." In his view, human security may be threatened by "the biologic revolution." He notes tht just as the "nuclear reality" has led to the term "omnicide," and environmental pollution to "ecocide," biological research may lead to "genecide."

As noted in my Decision document (FEDERAL REGISTER,) July 28, 1978), NIH has been asked to provide a forum for dealing with social issues relatig to "genetic engincering." The concerns of this witness may be taken in the same context. My Decision notes that NIH has been addressing the policy questions involving the safety of this research, not the "potential future application * * * to the altering of the genetic character of higher forms of life, including man * * *. In light of public concern, a study is warranted of the ethical, legal, and social implications of these techniques. The National Commission for Protection of Human Subjects of Biomedical and Behavioral Research considered, but was unable to initiate, a study * * *." Such a study might be considered by the Department's newly created Ethical Advisory Board. It could also be a key priority for the National Commission for the Protection of Human Subjects, which was reauthorized by the Congress before adjournment of this session.

APPENDIX II—FEDERAL INTERAGENCY ADVISORY COMMITTEE ON RECOMBINANT DNA RESEARCH, OCTOBER 1978

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APPENDIX III

EXCHANGE OF LETTERS BETWEEN SENATORS AND SECRETARY CALIFANO

[Letter to Senator Kennedy attached; similar letters were sent to the five other Senators]

UNITED STATES SENATE,
Washington, D.C., June 1, 1978

Hon. JOSEPH A. CALIFANO, JR.,
Secretary of Health, Education and Welfare, Department of Health, Education and Welfare, Washington, D.C. 20201.

DEAR MR. SECRETARY: Since 1976 four committees of the House and Senate have held nine series of hearings to consider the issues relating to recombinant DNA research. These extended and thorough inquiries have shown that, with respect to the research they support and conduct, the National Institutes of Health have taken a properly cautious approach by prohibiting certain presumably hazardous experiments, requiring certification of the safety of host-vector systems, prescribing physical and biological containment measures for the con-

duct of permissible experiments, and providing for changes in these restrictions as further scientific evidence resolves the uncertainties about the health and environmental effects of using recombinant DNA techniques.

Evidence accumulated in the past year, rather than revealing any hazards associated with these experiments, points to a high level of safety in the use of the predominant host organism, the K 12 strain of *E. coli*. The NIH Recombinant DNA Molecule Program Advisory Committee has recommended changes in the Institute's research guidelines to reflect this evidence, and these recommendations are being considered by Director Fredrickson. Other hosts and vectors have received less scrutiny, and uncertainty remains about risks that may be associated with future applications of the technology. These uncertainties justify continuing to require certain precautions in recombinant DNA work.

However, the hearings have also underscored the need to correct deficiencies in the present system of regulation. Privately supported research activities are not subject to monitoring by NIH nor to sanctions for failure to comply with the guidelines. Application of the NIH standards by other Federal agencies is voluntary. As Director Fredrickson has stated on several occasions, it is doubtful this enforcement by the principal Federal sponsor of recombinant DNA research—NIH—is appropriate. Procedures for revising the standards and exempting certain experiments should be clarified. It is important to ensure the accountability of institutions and investigators, particularly if they are to assume greater responsibility for monitoring compliance. The Federal Government should anticipate commercial applications of recombinant DNA techniques and the concerns they are likely to raise.

In view of these developments and in view of the heavy legislative schedule of the Senate and the Human Resources Committee, we are writing to inquire whether the deficiencies in the present regulatory system can be remedied through executive action in the event final agreement on legislation is not possible. Specifically, it would seem possible to shift monitoring and enforcement responsibilities from NIH to a more appropriate agency within the Department of Health, Education, and Welfare. It would also seem possible to remedy the problems of accountability and of coverage in the process of revising the recombinant DNA guidelines. On the basis of the survey of existing statutory authorities conducted by the Committee on Commerce, Science and Transportation, there seems to be adequate authority to regulate the commercial application of products developed through recombinant DNA technology. There is, however, need for more effective coordination among Federal agencies in the implementation of these authorities.

In this regard, you expressed to Senator Stevenson in your letter of February 27, 1978, that the Food and Drug Administration "• • • could, under existing authority, require any firm seeking approval of a product which may be the end product of recombinant DNA research to certify to the Agency that it has complied with the NIH guidelines on recombinant DNA." You noted also that FDA has authority to inspect firms making such certification to assure compliance with the NIH guidelines. This statement is important because most, if not all, recombinant DNA research by the private sector is being conducted by pharmaceutical companies with the objective of developing products that would be marketed in accordance with FDA regulations. A decision by the Administration to use this existing authority would bring the large majority of privately funded recombinant DNA research activities under the NIH guidelines. Is the Administration prepared to use the authority cited in your February 27th letter?

Finally, it has been suggested that section 361 of the Public Health Service Act provides sufficient authority to promulgate regulations covering recombinant DNA research conducted by the private sector with non-Federal funds. Although you have expressed the view that specific legislative authority is preferable to using the authority of section 361, we are raising the issue again for three reasons: (1) The need for new legislation is less clear than it was one year ago when the initial bills were introduced, (2) the existing regulatory deficiencies relating to Federally-supported research can be remedied by executive action, and (3) the heavy legislative schedule may preclude action in this session of Congress. In view of these developments, it seems prudent to explore the willingness of the Executive Branch to use the authority of section 361 to cover privately-funded recombinant DNA research. In addition, we request that you solicit a legal opinion from the Department of Justice as to the use of section 361 in this manner.

There is an additional factor to consider. In the past, Congress has been reluctant to extend statutory control over a specific field of scientific investigation unless such authority was absolutely necessary to protect the public's health and safety. In view of the scientific evidence accumulated during the past year, it is not possible to reach this conclusion in the case of recombinant DNA research. If the deficiencies discussed above could be corrected through executive action—by use of existing powers of FDA and/or the authority of section 361—there would be no reason to legislate new statutory controls.

In the event these executive actions were implemented, we would recommend that an appropriate group of experts and lay persons, such as the advisory committee to the NIH Director, continue to monitor the scientific evidence relating to the hypothetical risks of recombinant DNA research. If evidence indicating actual risks were to be developed, Congress could once again consider the need for legislation.

Since we are presently considering the legislative agenda for the balance of this session, we would appreciate your prompt response to this inquiry.

Sincerely,

EDWARD M. KENNEDY,
Chairman, Subcommittee on Health and Scientific Research.

JACOB K. JAVITS,
Ranking Minority Member, Committee on Human Resources.

GAYLORD NELSON,
Member, Committee on Human Resources.

ADLAI E. STEVENSON,
Chairman, Subcommittee on Science, Technology and Space.

HARRISON A. WILLIAMS, JR.,
Chairman, Committee on Human Resources.

RICHARD S. SCHWEIKER,
Ranking Minority Member, Subcommittee on Health and Scientific Research.

THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE,
Washington, D.C., September 12, 1978.

Hon. EDWARD M. KENNEDY,
Chairman, Subcommittee on Health and Scientific Research, Committee on Human Resources, United States Senate, Washington, D.C. 20510

DEAR TED: Thank you for your letter in which you have raised a number of thoughtful questions concerning the need for legislation to regulate recombinant DNA research.

As you state in your letter, new scientific information, particularly on the safety of *E. coli* K-12 (the principal organism used in these experiments), indicates that extensive regulation in this research area may be unwarranted. Indeed, there is additional evidence that many recombinant DNA manipulations in the laboratory may be similar to events that occur in nature.

In view of these scientific developments, you raise the question as to whether legislation is necessary or whether existing statutory authority would be sufficient for purposes of regulation. You cite specifically the regulatory authority of the FDA and of the Public Health Service Act (Section 361).

The Department does not intend to invoke existing statutory authorities to regulate DNA activities at this time. If an emergency were to occur before passage of legislation, the Department could reconsider this position in order to take action on an interim basis. But, we continue to support legislation if it embodies the moderate approach of H.R. 11192. The virtue of such legislation is that it n. v include a number of specific provisions that permit useful flexibility in implementing regulations. Such provisions include:

- the promotion of uniform national standards,
- clear authority for the Secretary in relationship to other Federal laws,
- avoidance of normal administrative procedures for initial application of NIH Guidelines and waiver of the Administrative Procedures Act (APA) for issuance of administrative regulations, and authority for the Secretary to waive regulatory requirements for activities that pose no significant risk to health or the environment.

In recommending legislation, the Federal Interagency Committee on Recombinant DNA Research reviewed all existing statutory authority and found that none could provide for comprehensive regulation of these activities. The Interagency Committee noted that under Section 361 "there would presumably have to be a reasonable basis for concluding that the products of all re-

combinant DNA research cause or may cause human disease. Such a conclusion would undoubtedly be tenuous at best, and it is unlikely that resulting requirements could be effectively imposed and enforced."

Your letter suggested that we seek a legal opinion from the Department of Justice on the use of Section 361. Justice is represented in the Interagency Committee and has participated in the review and recommendations concerning existing statutory authorities, including Section 361.

The authorities of the Food and Drug Administration (FDA) were reviewed by the Committee; but inasmuch as recombinant DNA research has not yet reached the stage where it has yielded products to be regulated by FDA, it was agreed that FDA probably does not have authority to impose requirements on such research at present.

On July 28, the Department published proposed revisions to the Guidelines on recombinant DNA research for 60 days of comment. In addition, I have asked General Counsel Peter Libassi to serve as Chairman and Dr. Donald Fredrickson as Vice Chairman of a September 15 public hearing on these proposed revisions. Analysis of written and oral comments will proceed as quickly as possible, with final issuance of the revised Guidelines expected before the first of December.

A number of proposed changes in the Guidelines would permit, on a voluntary basis, registration of activities and NIH certification of new host-vector systems from the private sector. Protection would be provided for proprietary an patent information for these private sector activities. Registration of recombinant DNA projects, irrespective of source of funding, would be required of institutions receiving NIH support for recombinant DNA research. By these means, a national registry of all Federal and private sector activities may evolve.

The Interagency Committee has been an invaluable forum for developing coherent and coordinated policies through the representation of all the relevant research and regulatory agencies, and has served to ensure a commonality of standards. This Committee should continue to provide such oversight for the development of Federal policies and to ensure institutional compliance with the NIH Guidelines. Other advisory committees, both technical and public, must continue. The Recombinant DNA Advisory Committee will have a continuing role, and as you suggest in your letter, the public Advisory Committee to the Director, NIH, should continue to consider recommendations from the technical group.

The NIH and the Center for Disease Control (CDC) will continue to work closely as they have done over the past 18 months concerning safety aspects of the Guidelines. For example, NIH, in conjunction with CDC, has been developing mechanisms for assisting institutions in managing possible laboratory emergencies and for providing direct assistance when appropriate. Indeed, NIH and CDC are collaborating in a revision of the CDC Classification of Etiologic Agents on the Basis of Hazards—a classification that underpins some of the safety requirements of the Guidelines. Also, these agencies are reviewing packaging and shipping requirements relavant to recombinant DNA activities.

Close cooperation and consultation with the Food and Drug Administration and the Environmental Protection Agency will also be essential, since the regulatory authority of these agencies will come into play when recombinant DNA research inventions are ready for commercial development. The Occupational Safety and Health Administration will exercise its regulatory authority in the workplace.

We are pleased with the progress made in the absence of legislation and believe that invocation of existing authorities, however appropriate, would not contribute materially to our objectives. Only passage of legislation embodying the features cited here would, in our opinion, justify the change from a voluntary to a regulatory approach. Should the Senate choose to act, I would strongly urge adoption of an approach similar to H.R. 11192.

Sincerely,

JOSEPH A. CALIFANO, Jr.

[FR Doc. 78-35532 Filed 12-21-78; 8:45 am]

federal register

FRIDAY, DECEMBER 22, 1978
PART VII

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES

[4110-08-M]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES

DECEMBER 1978.

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I. SCOPE OF THE GUIDELINES

I-A. *Purpose.* The purpose of these Guidelines is to specify practices for constructing and handling (i) recombinant DNA molecules and (ii) organisms and viruses containing recombinant DNA molecules.

I-B. *Definition of Recombinant DNA Molecules.* In the context of these Guidelines, recombinant DNA molecules are defined as either (i) molecules which are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or (ii) DNA molecules that result from the replication of those described in (i) above.

I-C. *General Applicability.* See Section IV-B.

I-D. *Prohibitions.* The following experiments are not to be initiated at the present time:

I-D-1. Formation of recombinant DNAs derived from the pathogenic organisms classified[1] as Class 3, 4, or 5[2] or from cells known [2A] to be infected with such agents, regardless of the host-vector system used.

I-D-2. Deliberate formation of recombinant DNAs containing genes for the biosynthesis of toxins potent for vertebrates [2A] (e.g., botulinum or diphtheria toxins; venoms from insects, snakes, etc.).

I-D-3. Deliberate creation by the use of recombinant DNA of a plant pathogen with increased virulence and host range beyond that which occurs by natural genetic exchange. [2A]

I-D-4. Deliberate release into the environment of any organism containing recombinant DNA.

I-D-5. Deliberate transfer of a drug resistence trait to microorgansims that are not known to acquire it naturally, if such acquisition could compromise the use of a drug to control disease agents in human or veterinary medicine or agriculture. [2A]

I-D-6. Large-scale experiments (e.g., more than 10 liters of culture) with organisms containing recombinant DNAs, unless the recombinant DNAs are rigorously characterized and the absence of harmful sequences established [3]. (See Section IV-E-1-b-(3)-(d).)

We differentiate between small- and large-scale experiments with organisms containing recombinant DNAs because the probability of escape from containment barriers normally increases with increasing scale.

Experiments in these categories may be excepted[4] from the prohibitions (and will at that time be assigned appropriate levels of physical and biological containment) provided that these experiments are expressly approved by the Director, NIH, with advice of the Recombinant DNA Advisory Committee after appropriate notice and opportunity for public comment. (Section IV-E-1-b-(1)-(e).)

I-E. *Exemptions.* It must be emphasized that the following exemptions[4] are not meant to apply to experiments described in the Section I-D-1 to I-D-5 as being prohibited.

The following recombinant DNA molecules are exempt from these Guidelines, and no registration with NIH is necessary:

I-E-1. Those that are not in organisms or viruses.[5]

I-E-2. Those that consist entirely or DNA segments from a single nonchromosomal or viral DNA source, though

one or more of the segments may be a synthetic equivalent.

I-E-3. Those that consist entirely of DNA from a prokaryotic host, including its indigenous plasmids or viruses, when propagated only in that host (or closely related strain of the same species) or when transferred to another host by well-established physiological means; also those that consist entirely of DNA from a eukaryotic host, including its chloroplasts, mitochondria, or plasmids (but excluding viruses), when propagated only in that host (or a closely related strain of the same species).

I-E-4. Certain specified recombinant DNA molecules that consist entirely of DNA segments from different species that exchange DNA by known physiological processes, though one or more of the segments may be a synthetic equivalent. A list of such exchangers will be prepared and periodically revised by the Director, NIH, with advice of the Recombinant DNA Advisory Committee, after appropriate notice and opportunity for public comment. (See Section IV-E-1-b-(1)-(d).) Certain classes are exempt as of publication of these Revised Guidelines. The list is in Appendix A. An updated list may be obtained from the Office of Recombinant DNA Activities, National Institutes of Health, Bethesda, Maryland 20014.

I-E-5. Other classes of recombinant DNA molecules, if the Director, NIH, with advice of the Recombinant DNA Advisory Committee, after appropriate notice and opportunity for public comment, finds that they do not present a significant risk to health or the environment. (See Section IV-E-1-b-(1)-(d).)

I-F. *General Definitions.* See Section IV-C.

II. Containment

Effective biological safety programs have been operative in a variety of laboratories for many years. Considerable information therefore already exists for the design of physical containment facilities and the selection of laboratory procedures applicable to organisms carrying recombinant DNAs. [6-19] The existing programs rely upon mechanisms that, for convenience, can be divided into two categories: (i) A set of standard practices that are generally used in microbiological laboratories, and (ii) special procedures, equipment, and laboratory installations that provide physical barriers which are applied in varying degrees according to the estimated biohazard.

Experiments on recombinant DNAs, by their very nature, lend themselves to a third containment mechanism—namely, the application of highly specific biological barriers. In fact, natural barriers do exist which limit either (i) the infectivity of a *vector*, or *vehicle*, (plasmid or virus) for specific hosts or (ii) its dissemination and survival in the environment. The vectors that provide the means for replication of the recombinant DNAs and/or the host cells in which they replicate can be genetically designed to decrease by many orders of magnitude the probability of dissemination of recombinant DNAs outside the laboratory.

As these three means of containment are complementary, different levels of containment appropriate for experiments with different recombinants can be established by applying various combinations of the physical and biological barriers along with a constant use of the standard practices. We consider these categories of containment separately here in order that such combinations can be conveniently expressed in the Guidelines.

In constructing these Guidelines, it was necessary to define boundary conditions for the different levels of physical and biological containment and for the classes of experiments to which they apply. We recognize that these definitions do not take into account all existing and anticipated information on special procedures that will allow particular experiments to be carried out under different conditions than indicated here without affecting risk. Indeed, we urge that individual investigators devise simple and more effective containment procedures and that investigators and institutional biosafety committees recommend changes in the Guidelines to permit their use.

II-A. *Standard Practices and Training.* The first principle of containment is a strict adherence to good microbiological practices. [6-15] Consequently, all personnel directly or indirectly involved in experiments on recombinant DNAs must receive adequate instruction. (see Sections IV-D-1-g, IV-D-5-d and IV-D-8-b.). This shall as a minimum include instructions in aseptic techniques and in the biology of the organisms used in the experiments, so that the potential biohazards can be understood and appreciated.

Any research group working with agents with a known or potential biohazard shall have an emergency plan which describes the procedures to be followed if an accident contaminates personnel or the environment. The principal investigator must ensure that everyone in the laboratory is familiar with both the potential hazards of the work and the emergency plan. (See Sections IV-D-5-e and IV-D-3-d.) If a research group is working with a known pathogen where there is an effective vaccine it should be made available to all workers. Where serological monitoring is clearly appropriate it shall be provided. (See Sections IV-D-1-h and IV-D-8-c.)

II-B. *Physical Containment Levels.* The objective of physical containment is to confine organisms containing recombinant DNA molecules, and thus to reduce the potential for exposure of the laboratory worker, persons outside of the laboratory, and the environment to organisms containing recombinant DNA molecules. Physical containment is achieved through the use of laboratory practices, containment equipment, and special laboratory design. Emphasis is placed on primary means of physical containment which are provided by laboratory practices and containment equipment. Special laboratory design provides a secondary means of protection against the accidental release of organisms outside the laboratory or to the environment. Special laboratory design is used primarily in facilities in which experiments of moderate to high potential hazard are performed.

Combinations of laboratory practices, containment equipment, and special laboratory design can be made to achieve different levels of physical containment. Four levels of physical containment, which are designated as P1, P2, P3, and P4, are described. It should be emphasized that the descriptions and assignments of physical containment detailed below are based on existing approaches to containment of pathogenic organisms. For example, the "Classification of Etiologic Agents on the Basis of Hazard," [7] prepared by the Center for Disease Control, describes four general levels which roughly correspond to our descriptions for P1, P2, P3, and P4; and the National Cancer Institute describes three levels for research on oncogenic viruses which roughly correspond to our P2, P3, and P4 levels. [8]

It is recognized that several different combinations of laboratory practices, containment equipment, and special laboratory design may be appropriate for containment of specific research activities. The Guidelines, therefore, allow alternative selections of primary containment equipment within facilities that have been designed to provide P3 and P4 levels of physical containment. The selection of alternative methods of primary containment is dependent, however, on the level of biological containment provided by the host-vector system used in the experiment. Consideration will also be given by the Director, NIH, with the advice of the Recombinant DNA Advisory Committee to other combinations which achieve an equivalent level of containment. (See Section IV-E-1-b-(2)-(b).) Additional material on physical containment for plant host-vector systems is found in Sections III-C-3 and III-C-4.

II-B-1. *P1 Level.*

II-B-1-a. *Laboratory Practices.*

II-B-1-a-(1). Laboratory doors shall be kept closed while experiments are in progress.

II-B-1-a-(2). Work surfaces shall be decontaminated daily, and immediately following spills of organisms containing recombinant DNA molecules.

II-B-1-a-(3). All biological wastes shall be decontaminated before disposal. Other contaminated materials, such as glassware, animal cages, and laboratory equipment, shall be decontaminated before washing, reuse, or disposal.

II-B-1-a-(4). Mechanical pipetting devices shall be used; pipetting by mouth is prohibited.

II-B-1-a-(5). Eating, drinking, smoking, and storage of foods are not permitted in the laboratory area in which recombinant DNA materials are handled.

II-B-1-a-(6). Persons shall wash their hands after handling organisms containing recombinant DNA molecules and when they leave the laboratory.

II-B-1-a-(7). Care shall be taken in the conduct of all procedures to minimize the creation of aerosols.

II-B-1-a-(8). Contaminated materials that are to be decontaminated at a site away from the laboratory shall be placed in a durable leak-proof container, which is closed before removal from the laboratory.

II-B-1-a-(9). An insect an rodent control program shall be instituted.

II-B-1-a-(10). The use of laboratory gowns, coats, or uniforms is discretionary with the laboratory supervisor.

II-B-1-a-(11). Use of the hypodermic needle and syringe shall be avoided when alternative methods are available.

II-B-1-a-(12). The laboratory shall be kept neat and clean.

II-B-1-b. *Containment Equipment.* Special containment equipment is not required at the P1 level.

II-B-1-c. *Special Laboratory Design.* Special laboratory design is not required at the P1 level.

II-B-2. *P2 Level.*

II-B-2-a. *Laboratory Practices.*

II-B-2-a-(1). Laboratory doors shall be kept closed while experiments are in progress.

II-B-2-a-(2). Work surfaces shall be decontaminated daily, and immediately following spills of organisms containing recombitant DNA molecules.

II-B-2-a-(3). All laboratory wastes shall be steam-sterilized (autoclaved) before disposal. Other contaminated materials such as glassware, animal cages, laboratory equipment, and radioactive wastes shall be decontaminated by a means demonstrated to be effective before washing, reuse, or disposal.

II-B-2-a-(4). Mechanical pipetting devices shall be used; pipetting by mouth is prohibited.

II-B-2-a-(5). Eating, drinking, smoking, and storage of food are not permitted in the laboratory area in which recombinant DNA materials are handled.

II-B-2-a-(6). Persons shall wash their hands after handling organisms containing recombinant DNA molecules and when they leave the laboratory.

II-B-2-a-(7). Care shall be exercised to minimize the creation of aerosols. For example, manipulations such as inserting a hot inoculating loop or needle into a culture, flaming an inoculation loop or needle so that it splatters, and forceful ejection of fluids from pipettes or syringes shall be avoided.

II-B-2-a-(8). Contaminated materials that are to be steam sterilized (autoclaved) or decontaminated at a site away from the laboratory shall be placed in a durable leak-proof container, which is closed before removal from the laboratory.

II-B-2-a-(9). Only persons who have been advised of the nature of the research being conducted shall enter the laboratory.

II-B-2-a-(10). The universal biohazard sign shall be posted on all laboratory access doors when experiments requiring P2 containment are in progress. Freezers and refrigerators or other units used to store organisms containing recombinant DNA molecules shall also be posted with the universal biohazard sign.

II-B-2-a-(11). An insect and rodent control program shall be instituted.

II-B-2-a-(12). The use of laboratory gowns, coats, or uniforms is required. Laboratory clothing shall not be worn to the lunch room or outside of the building in which the laboratory is located.

II-B-2-a-(13). Animals not related to the experiment shall not be permitted in the laboratory.

II-B-2-a-(14). Use of the hypodermic needle and syringe shall be avoided when alternative methods are available.

II-B-2-a-(15). The laboratory shall be kept neat and clean.

II-B-2-a-(16). Experiments of lesser biohazard potential can be carried out concurrently in carefully demarcated areas of the same laboratory.

II-B-2-b. *Containment Equipment.* Biological safety cabinets[20] shall be used to contain aerosol-producing equipment, such as blenders, lyophilizers, sonicators, and centrifuges, when used to process organisms containing recombinant DNA molecules, except where equipment design provides for containment of the potential aerosol. For example, a centrifuge may be operated in the open if a sealed head or safety centrifuge cups are used.

II-B-2-c. *Special Laboratory Design.* An autoclave for sterilization of wastes and contaminated materials shall be available in the same building in which organisms containing recombinant DNA molecules are used.

II-B-3. *P3 Level.*

II-B-3-a. *Laboratory Practices.*

II-B-3-a-(1). Laboratory doors shall be kept closed while experiments are in progress.

II-B-3-a-(2). Work surfaces shall be decontaminated following the completion of the experimental activity, and immediately following spills of organisms contining recombinant DNA molecules.

II-B-3-a-(3). All laboratory wastes shall be steam-sterilized (autoclaved) before disposal. Other contaminated materials, such as glassware, animal cages, laboratory equipment, and radioactive wastes, shall be decontaminated by a method demonstrated to be effective before washing, reuse, or disposal.

II-B-3-a-(4). Mechanical pipetting devices shall be used; pipetting by mouth is prohibited.

II-B-3-a-(5). Eating, drinking, smoking, and storage of food are not permitted in the laboratory area in which recombinant DNA materials are handled.

II-B-3-a-(6). Persons shall wash their hands after handling organisms containing recombinant DNA molecules and when they leave the laboratory.

II-B-3-a-(7). Care shall be exercised to minimize the creation of aerosols. For example, manipulations such as inserting a hot inoculating loop or needle into a culture, flaming an inoculation loop or needle so that it splatters, and forceful ejection of fluids from pipettes or syringes shall be avoided.

II-B-3-a-(8). Contaminated materials that are to be steam-sterilized (autoclaved) or decontaminated at a site away from the laboratory shall be placed in a durable leak-proof container, which is closed before removal from the laboratory.

II-B-3-a-(9). Entry into the laboratory shall be through a controlled access area. Only persons who have been advised of the nature of the research being conducted shall enter the controlled access area. Only persons required on the basis of program or support needs shall be authorized to enter the laboratory. Such persons shall be advised of the nature of the research being conducted before entry, and shall comply with all required entry and exit procedures.

II-B-3-a-(10). Persons under 16 years of age shall not enter the laboratory.

II-B-3-a-(11). The universal biohazard sign shall be posted on the controlled access area door and on all laboratory doors when experiments requiring P3-level containment are in progress. Freezers and refrigerators or other units used to store organisms containing recombinant DNA molecules shall also be posted with the universal biohazard sign.

II-B-3-a-(12). An insect and rodent control program shall be instituted.

II-B-3-a-(13). Laboratory clothing that protects street clothing (e.g., long-sleeve solid-front or wrap-around gowns, no-button or slipover jackets) shall be worn in the laboratory. Front-button laboratory coats are unsuitable. Laboratory clothing shall not be worn outside the laboratory and shall be decontaminated before it is sent to the laundry.

II-B-3-a-(14). Raincoats, overcoats, topcoats, coats, hats, caps, and such street outer-wear shall not be kept in the laboratory.

II-B-3-a-(15). Gloves shall be worn when handling materials requiring P3 containment. They shall be removed aseptically immediately after the handling procedure and decontaminated.

II-B-3-a-(16). Animals and plants not related to the experiment shall not be permitted in the laboratory.

II-B-3-a-(17). Vacuum outlets shall be protected by filter and liquid disinfectant traps.

II-B-3-a-(18). Use of hypodermic needle and syringe shall be avoided when alternative methods are available.

II-B-3-a-(19). The laboratory shall be kept neat and clean.

II-B-3-a-(20). If experiments involving other organisms which require lower levels of containment are to be conducted in the same laboratory concurrently with experiments requiring P3-level physical containment, they shall be conducted in accordance with all P3-level laboratory practices.

II-B-3-b. *Containment Equipment.*

II-B-3-b-(1). Biological safety cabinets [20] shall be used for all equipment and manipulations that produce aerosols—e.g., pipetting, dilutions, transfer operations, plating, flaming, grinding, blending, drying, sonicating, shaking, centrifuging—where these procedures involve organisms containing recombinant DNA molecules, except where equipment design provides for containment of the potential aerosol.

II-B-3-b-(2). Laboratory animals held in a P3 area shall be housed in partial-containment caging systems, such as Horsfall units [19A], open cages placed in ventilated enclosures, solid-wall and -bottom cages covered by filter bonnets, or solid-wall and -bottom cages placed on holding racks equipped with ultraviolt radiation lamps and reflectors. (Note: Conventional caging systems may be used, provided that all personnel wear appropriate personal protective devices. These shall include, at a minimum, wrap-around gowns, head covers, gloves, shoe covers, and respirators. All personnel shall shower on exit from areas where these devices are required.)

II-B-3-b-(3). *Alternative Selection of Containment Equipment.* Experimental procedures involving a host-vector system that provides a one-step higher level of biological containment than that specified in Part III can be conducted in the P3 laboratory using containment equipment specified for the P2 level of physical containment. Experimental procedures involving a host-vector system that provides a one-step lower level of biological containment than that specified in Part III can be conducted in the P3 laboratory using containment equipment specified for the P4 level of physical containment. Alternative combinations of containment safeguards are shown in Table I.

TABLE I.—*Combinations of Containment Safeguards*

Classification of experiment according to Guidelines		Alternate combinations of physical and biological containment			
		Physical Containment			
Physical containment	Biological* containment	Laboratory design specified for:	Laboratory practices specified for:	Containment equipment specified for:	Biological containment
P3	HV3	P3	P3	P3	HV3
P3	HV3	P3	P3	P4	HV2
P3	HV2	P3	P3	P3	HV2
P3	HV2	P3	P3	P2	HV3
P3	HV2	P3	P3	P4	HV1
P3	HV1	P3	P3	P3	HV1
P3	HV1	P3	P3	P2	HV2

*See section II-D for description of biological containment.

II-B-3-c. *Special Laboratory Design.*

II-B-3-c-(1). The laboratory shall be separated by a controlled access area from areas that are open to unrestricted traffic flow. A controlled access area is an anteroom, a change room, an air lock or any other double-door arrangement that separates the laboratory from areas open to unrestricted traffic flow.

II-B-3-c-(2). The surfaces of walls, floors, and ceilings shall be readily cleanable. Penetrations through these surfaces shall be sealed or capable of being sealed to facilitate space decontamination.

II-B-3-c-(3). A foot-, elbow-, or automatically-operated handwashing facility shall be provided near each primary laboratory exit area.

II-B-3-c-(4). Windows in the laboratory shall be sealed.

II-B-3-c-(5). An autoclave for sterilization of wastes and contaminated materials shall be available in the same building (and preferably within the controlled laboratory area) in which organisms containing recombinant DNA molecules are used.

II-B-3-c-(6). The laboratory shall have a ventilation system that is capable of controlling air movement. The movement of air shall be from areas of lower contamination potential to areas of higher contamination potential (i.e. from the controlled access area to the laboratory area). If the ventilation system provides positive pressure supply air, the system shall operate in a manner that prevents the reversal of the direction of air movement or shall be equipped with an alarm that would be actuated in the event that reversal in the direction of air movement were to occur. The exhause air from the laboratory area shall not be recirculated to other areas of the building unless the exhaust air is filtered by HEPA filters or equivalent. The exhaust air from the laboratory area can be discharged to the outdoors without filtration or other means for effectively reducing an accidental aerosol burden provided that it can be dispersed clear of occupied buildings and air intakes.

II-B-3-c-(7). The treated exhaust-air from Class I and Class II biological safety cabinets [20] may be discharged either to the laboratory or to the outdoors. The treated exhaust-air from a class III cabinet shall be discharged directly to the outdoors. If the treated exhaust-air from these cabinets is to be discharged to the outdoors through a building exhaust air system, it shall be connected to this system so as to avoid any interference with the air

balance of the cabinet and the building ventilation system.

II-B-4. *P4 Level.*

II-B-4-a. *Laboratory Practices.*

II-B-4-a-(1). Laboratory doors shall be kept closed while experiments are in progress.

II-B-4-a-(2). Work surfaces shall be decontaminated following the completion of the experimental activity and immediately following spills of organisms containing recombinant DNA molecules.

II-B-4-a-(3). All laboratory wastes shall be steam-sterilized (autoclaved) before disposal. Other contaminated materials such as glassware, animal cages, laboratory equipment, and radioactive wastes shall be decontaminated by a method demonstrated to be effective before washing, reuse, or disposal.

II-B-4-a-(4). Mechanical pipetting devices shall be used; pipetting by mouth is prohibited.

II-B-4-a-(5). Eating, drinking, smoking, and storage of food are not permitted in the P4 facility.

II-B-4-a-(6). Persons shall wash their hands after handling organisms containing recombinant DNA molecules and when they leave the laboratory.

II-B-4-a-(7). Care shall be exercised to minimize the creation of aerosols. For example, manipulations such as inserting a hot inoculating loop or needle into a culture, flaming an inoculation loop or needle so that it splatters, and forceful ejection of fluids from pipettes or syringes shall be avoided.

II-B-4-a-(8). Biological materials to be removed from the P4 facility in a viable or intact state shall be transferred to a nonbreakable sealed container, which is then removed from the P4 facility through a pass-through disinfectant dunk tank or fumigation chamber.

II-B-4-a-(9). No materials, except for biological materials that are to remain in a viable or intact state, shall be removed from the P4 facility unless they have been steam-sterilized (autoclaved) or decontaminated by a means demonstrated to be effective as they pass out of the P4 facility. All wastes and other materials as well as equipment not damaged by high temperature or steam shall be steam sterilized in the double-door autoclave of the P4 facility. Other materials which may be damaged by temperature or steam shall be removed from the P4 facility through a pass-through fumigation chamber.

II-B-4-a-(10). Materials within the Class III cabinets shall be removed from the cabinet system only after being steam-sterilized in an attached double-door autoclave or after being contained in a nonbreakable sealed container, which is then passed through a disinfectant dunk tank or a fumigation chamber.

II-B-4-a-(11). Only persons whose entry into the P4 facility is required to meet program or support needs shall be authorized to enter. Before entering, such persons shall be advised of the nature of the research being conducted and shall be instructed as to the appropriate safeguards to ensure their safety. They shall comply with instructions and all other required procedures.

II-B-4-a-(12). Persons under 18 years of age shall not enter the P4 facility.

II-B-4-a-(13). Personnel shall enter into and exit from the P4 facility only through the clothing change and shower rooms. Personnel shall shower at each egress from the P4 facility. Air locks shall not be used for personnel entry or exit except for emergencies.

II-B-4-a-(14). Street clothing shall be removed in the outer side of the clothing-change area and kept there. Complete laboratory clothing, including undergarments, head cover, shoes, and either pants and shirts or jumpsuits, shall be used by all persons who enter the P4 facility. Upon exit, personnel shall store this clothing in lockers provided for this purpose or discard it into collection hampers before entering the shower area.

II-B-4-a-(15). The universal biohazard sign is required on the P4 facility access doors and on all interior doors to individual laboratory rooms where experiments are conducted. The sign shall also be posted on freezers, refrigerators, or other units used to store organisms containing recombinant DNA molecules.

II-B-4-a-(16). An insect and rodent control program shall be instituted.

II-B-4-a-(17). Animals and plants not related to the experiment shall not be permitted in the laboratory in which the experiment is being conducted.

II-B-4-a-(18). Vacuum outlets shall be protected by filter and liquid disinfectant traps.

II-B-4-a-(19). Use of the hypodermic needle and syringe shall be avoided when alternate methods are available.

II-B-4-a-(20). The laboratory shall be kept neat and clean.

II-B-4-a-(21). If experiments involving other organisms which require lower levels of containment are to be conducted in the P4 facility concurrently with experiments requiring P4-level containment, they shall be conducted in accordance with all P4-level laboratory practices specified in this section.

II-B-4-b. *Containment Equipment.*

II-B-4-b-(1). Experimental procedures involving organisms that require P4-level physical containment shall be conducted either in (i) a Class III cabinet system or in (ii) Class I or Class II cabinets that are located in a specially designed area in which all personnel are required to wear one-piece positive-pressure isolation suits.

II-B-4-b-(2). Laboratory animals involved in experiments requiring P4-level physical containment shall be housed either in cages contained in Class III cabinets or in partial-containment caging systems (such as Horsfall units [19A], open cages placed in ventilated enclosures, or solid-wall and -bottom cages covered by filter bonnets, or solid-wall and -bottom cages placed on holding racks equipped with ultraviolet irradiation lamps and reflectors) that are located in a specially designed area in which all personnel are required to wear one-piece positive-pressure suits.

II-B-4-b-(3). *Alternative Selection of Containment Equipment.* Experimental procedures involving a host-vector system that provides a one-step higher level of biological containment than that specified in Part III can be conducted in the P4 facility using containment equipment requirements specified for the P3 level of physical containment. Alternative combinations of containment safeguards are shown in Table II.

TABLE II.—*Combinations of Containment Safeguards*

Classification of experiment according to Guidelines		Alternate combinations of physical and biological containment			
		Physical containment			
Physical containment	Biological* containment	Laboratory design specified for:	Laboratory practices specified for:	Containment equipment specified for:	Biological containment
P4	HV1	P4	P4	P4	HV1
P4	HV1	P4	P4**	P3	HV2

* See Section II-D for description of biological containment.** In this case gloves shall be worn, in addition to the clothing requirements specified in II-B-4-a-(14).

II-B-4-c. *Special Laboratory Design.*

II-B-4-c-(1). The laboratory shall be located in a restricted-access facility which is either a separate building or a clearly demarcated and isolated zone within a building. Clothing-change areas and shower rooms shall be provided for personnel entry and egress. These rooms shall be arranged so that personnel leave through the shower area to the change room. A double-door ventilated vestibule or ultraviolet air lock shall be provided for passage of materials, supplies, and equipment which are not brought into the P4 facility through the change room area.

II-B-4-c-(2). Walls, floors, and ceilings of the P4 facility are constructed to form an internal shell which readily allows vapor-phase decontamination and is animal- and insect-proof. All penetrations through these structures and surfaces are sealed. (The integrity of the walls, floors, ceilings, and penetration seals should ensure adequate containment of a vapor-phase decontaminant under static pressure conditions. This requirement does not imply that these surfaces must be airtight.)

II-B-4-c-(3). A foot-, elbow-, or automatically-operated handwashing facility shall be provided near the door within each laboratory in which experiments involving recombinant DNA are conducted in openface biological safety cabinets.

II-B-4-c-(4). Central vacuum systems are permitted. The system, if provided, shall not serve areas outside the P4 facility. The vacuum system shall include in-line HEPA filters near each use point or service cock. The filters shall be installed so as to permit in-place decontamination and replacement. Water supply and liquid and gaseous servies provided to the P4 facility shall be protected by devices that prevent backflow.

II-B-4-c-(5). Drinking water fountains shall not be installed in laboratory or animal rooms of the P4 facility. Foot-operated water fountains are permitted in the corridors of the P4 facility. The water service provided to such fountains shall be protected from the water services to the laboratory areas of the P4 facility.

II-B-4-c-(6). Laboratory doors shall be self-closing.

II-B-4-c-(7). A double-door autoclave shall be provided for sterilization of material passing out of the P4 facility. The autoclave doors shall be interlocked so that both doors will not be open at the same time.

II-B-4-c-(8). A pass-through dunk tank or fumigation chamber shall be provided for removal from the P4 facility of material and equipment that cannot be heat-sterilized.

II-B-4-c-(9). All liquid effluents from the P4 facility shall be collected and decontaminated before disposal. Liquid effluents from biological safety cabinets and laboratory sinks shall be sterilized by heat. Liquid effluents from the shower and hand washing facilities may be inactivated by chemical treatment. HEPA filters shall be installed in all vents from effluent drains.

II-B-4-c-(10). An individual supply and exhaust-air ventilation system shall be provided. The system shall maintain pressure differentials and directional air flow as required to ensure inflow from areas outside the facility toward areas of highest potential risk within the facility. The system shall be designed to prevent the reversal of air flow. The system shall sound an alarm in the event of system malfunction.

II-B-4-c-(11). Air within individual laboratories of the P4 facility may be recirculated if HEPA filtered.

II-B-4-c-(12). The exhaust air from the P4 facility shall be HEPA filtered and discharged to the outdoors so that it is dispersed clear of occupied buildings and air intakes. The filter chambers shall be designed to allow *in situ* decontamination before removal and to facilitate certification testing after replacement.

II-B-4-c-(13). The treated exhaust-air from Class I and Class II biological safety cabinets [20] may be discharged directly to the laboratory room environment or to the outdoors. The treated exhaust-air from Class III cabinets shall be discharged to the outdoors. If the treated exhaust-air from these cabinets is to be discharged to the outdoors through the P4 facility exhaust air system, it shall be connected to this system so as to avoid any interference with the air balance of the cabinets or the facility exhaust air system.

II-B-4-b-(14). As noted in Section II-B-4-c-(1), the P4 facility may contain specially designed areas in which all personnel are required to wear one-piece positive-pressure isolation suits. Such areas shall be airtight. The exhaust-air from the suit area shall be filtered by two sets of HEPA filters installed in series, and a duplicate filtration unit and exhaust fan shall be provided. The air pressure within the suit area shall be less than that in any adjacent area. An emergency lighting system, communication systems, and power source shall be provided. A double-door autoclave shall be provided for sterilization of all waste materials to be removed from the suit area.

Personnel who enter this area shall wear a one-piece positive-pressure suit that is ventilated by a life-support system. The life-support sysem shall be provided with alarms and emergency backup air. Entry to this area is through an airlock fitted with airtight doors. A chemical shower area shall be provided to decontaminate the surfaces of the suit before removal.

II-C. *Shipment.* Recombinant DNA molecules contained in an organism or virus shall be shipped only as an etiologic agent under requirements of the U.S. Public Health Service and the U.S. Department of Transportation (§ 72.25, Part 72, Title 42, and §§ 173.386-.388, Part 173, Title 49, U.S. Code of Federal Regulations) as specified below:

II-C-1. Recombinant DNA molecules contained in an organism or virus requiring P1, P2, or P3 physical containment, when offered for transportation or transported, are subject to all requirements of § 72.25(c)(1)-(5), Part 72, Title 42 CFR, and §§ 173.386-.388, Part 173, Title 49 CFR.

II-C-2. Recombinant DNA molecules contained in an organism or virus requiring P4 physical containment, when offerd for transportation or transported, are subject to the requirements listed above under II-C-1 and are also subject to § 72.25(c)(6), Part 72, Title 42 CFR.

II-C-3. Additional information on packaging and shipment is given in the "Laboratory Safety Monograph—A Supplement to the NIH Guidelines for Reombinant DNA Research."

II-D. *Biological Containment.*

II-D-1. *Levels of Biological Containment.* In consideration of biological containment, the vector (Plasmid, organelle, or virus) for the recombinant DNA and the host (bacterial, plant, or animal cell) in which the vector is propagated in the laboratory will be considered together. Any combination of vector and host which is to provide biological containment must be chosen or constructed so that the following types of "escape" are minimized: (i) Survival of the vector in its host outside the laboratory and (ii) transmission of the vector from the propagation host to other nonlaboratory hosts.

The following levels of biological containment (HV, or *Host-Vector*, systems) for prokaryotes will be established; specific criteria will depend on the organisms to be used. Eukaryotic host-vector systems are considered in Part III.

II-D-1-a. *HV1.* A host-vector system which provides a moderate level of containment. *Specific systems:*

II-D-1-a-(1). *EK1.* The host is always *E. Coli* K-12 or a derivative thereof, and the vectors include nonconjugative plasmids (e.g., pSC101, ColE1, or derivatives thereof [21-27]) and variants of bacteriophage, such as [28-33]. The *E. Coli* K-12 hosts shall not contain conjugation-proficient plasmids, whether autonomous or integrated, or generalized transducing phages.

II-D-1-a-(2). *Other Prokaryotes.* Hosts and vectors shall be, at a minimum, comparable in containment to *E. Col.* K-12 with a non conjugative plasmid or bacteriophage vector. The data to be considered and mechanism for approval of such HV1 systems are described below (Section II-D-2).

II-D-1-b. *HV2* These are host-vector systems shown to provide a high level of biological containment as demonstrated by data from suitable tests performed in the laboratory. Escape of the recombinant DNA either via survival of the organisms or via transmission of recombinant DNA to other organisms should be less than $1/10^8$ under specified conditions. *Specific systems:*

II-D-1-b-(1). For EK2 host-vector systems in which the vector is a plasmid, no more than one in 10^8 host cells should be able to perpetuate a cloned DNA fragment under the specified nonpermissive laboratory conditions designed to represent the natural environment, either by survival of the original host or as a consequence of transmission of the cloned DNA fragment.

II-D-1-b-(2). For EK2 host-vector systems in which the vector is a phage, no more than one in 10^8 phage particles should be able to perpetuate a cloned DNA fragment under the specified nonpermissive laboratory conditions designed to represent the natural environment either (i) as a prophage (in the inserted or plasmid form) in the laboratory host used for phage propagation or (ii) by surviving in natural environments and transferring a cloned DNA fragment to other hosts (or their resident prophages).

II-D-1-c. *HV3.* These are host-vector systems in which:

II-D-1-c-(1). All HV2 criteria are met.

II-D-1-c-(2). The vector is dependent on its propagation host or is highly defective in mobilizability. Reversion to host-independence must be less than $1/10^8$ per vector genome per generation.

II-D-1-c-(3). No markers conferring resistance to antibiotics commonly used clinically or in agriculture are carried by the vector, unless expression of such markers is dependent on the propagating host or on unique laboratory-controlled conditions or is blocked by the inserted DNA.

II-D-1-c-(4). The specified containment shown by laboratory tests has been independently confirmed by specified tests in animals, including primates, and in other relevant environments.

II-D-1-c-(5). The relevant genotypic and phenotypic traits have been independently confirmed.

II-D-2. *Certification of Host-Vector Systems.*

II-D-2-a. *Responsibility.* HV1 systems other than *E. coli* K-12, and HV2 and HV3 host-vector systems, may not be designated as such until they have been certified by the Director, NIH. Application for certification of a host-vector system is made by written application to the Office of Recombinant DNA Activities (ORDA), National Institutes of Health, Bethesda, Maryland 20014.

Host-vector systems that are proposed for certification will be reviewed by the NIH Recombinant DNA Advisory Committee (RAC). (See Section IV-E-1-b-(1)-(c).) This will first involve review of the data on construction, properties, and testing of the proposed host-vector system by a Working Group composed of one or more members of the RAC and other persons chosen because of their expertise in evaluating such data. The Committee will then evaluate the report of the Working Group and any other available information at a regular meeting. The Director, NIH is responsible for certification after receiving the advice of the RAC. Minor modifications of existing certified host-vector systems, where the modifications are of minimal or no consequence to the properties relevant to containment may be certified by the Director, NIH without review by the RAC. (See Section IV-E-1-b-(3)-(h).)

When new host-vector systems are certified, notice of the certification will be sent by ORDA to the applicant and to all IBCs and will be published in the *Recombinant DNA Technical Bulletin.* Copies of a list of all currently certified host-vector systems may be obtained from ORDA at any time.

The Director, NIH may at any time rescind the certification of any host-vector system. (See Section IV-E-1-b-(3)-(i).) If certification of a host-vector system is rescinded, NIH will instruct investigators to transfer cloned DNA into a different system, or use the clones at a higher physical containment level unless NIH determines that the already constructed clones incorporate adequate biological containment.

Certification of a given system does not extend to modifications of either the host or vector component of that system. Such modified systems must be independently certified by the Director, NIH. If modifications are minor, it may only be necessary for the investigator to submit data showing that the modifications have either improved or not impaired the major phenotypic traits on which the containment of the system depends. Substantial modifications of a certified system require the submission of complete testing data.

II-D-2-b. *Data To Be Submitted for Certification.*

II-D-2-b-(1). *HV1 Systems Other than E. Coli K-12.* The following types of data shall be submitted, modified as appropriate for the particular system under consideration: (i) A description of the organism and vector; the strain's natural habitat and growth requirements; its physiological properties, particularly those related to its reproduction and survival and the mechanisms by which it exchanges genetic information; the range of organisms with which this organism normally exchanges genetic information and what sort of information is exchanged; and any relevant information on its pathogenicity or toxicity. (ii) A description of the history of the particular strains and vectors to be used, including data on any mutations which render this organism less able to survive or transmit genetic information. (iii) A general description of the range of experiments contemplated, with emphasis on the need for developing such an HV1 system.

II-D-2-b-(2). *HV2 Systems.* Investigators planning to request HV2 certification for host-vector systems can obtain instructions from ORDA concerning data to be submitted [33A, 33B]. In general, the following types of data are required: (i) Description of construction steps, with indication of source, properties, and manner of introduction of genetic traits. (ii) Quantitative data on the stability of genetic traits that contribute to the containment of the system. (iii) Data on the survival of the host-vector system under non-permissive laboratory conditions designed to represent the relevant natural environment. (iv) Data on transmissibility of the vector and/or a cloned DNA fragment under both permissive and nonpermissive conditions. (v) Data on all other properties of the system which affect containment and utility, including information on yields of phage or plasmid molecules, ease of DNA isolation, and ease of transfection or transformation. (vi) In some cases, the investigator may be asked to submit data on survival and vector transmissibility from experiments in which the host-vector is fed to laboratory animals (e.g., rodents). Such *in vivo* data may be required to confirm the validity of predicting *in vivo* survival on the basis of *in vitro* experiments.

Data must be submitted in writing to ORDA. Ten to twelve weeks are normally required for review and circulation of the data prior to the meeting at which such data can be considered by the NIH Recombinant DNA Advisory Committee (RAC). Investigators are encouraged to publish their data on the construction, properties, and testing of proposed HV2 systems prior to consideration of the system by the RAC and its subcommittee. More spe-

cific instructions concerning the type of data to be submitted to NIH for proposed EK2 systems involving either plasmids or bacteriophage ● in *E. coli* K-12 are available from ORDA.

II-D-2-b-(3). *HV3 Systems.* Putative HV3 systems must, as the first step in certification, be certified as HV2 systems. Systems which meet the criteria given above under II-D-1-(c)-1, II-D-1-(c)-2, II-D-1-(c)-3 will then be recommended for HV3 testing. Tests to evaluate various HV2 host-vector systems for HV3 certification will be performed by contractors selected by NIH. These contractors will repeat tests performed by individuals proposing the HV2 system and, in addition, will conduct more extensive tests on conditions likely to be encountered in nature. The genotypic and phenotypic traits of HV2 systems will be evaluated. Tests on survival and transmissibility in and on animals, including primates, will be performed, as well as tests on survival in certain specified natural environments.

II-D-3. *Distribution of Certified Host-Vectors.* Certified HV2 and HV3 host-vector systems (plus appropriate control strains) must be obtained from the NIH or its designees, one of whom will be the investigator who developed the system. NIH shall announce the availability of the system by publication of notices in appropriate journals.

Plasmid vectors will be provided in a suitable host strain, and phage vectors will be distributed as small-volume lysates. If NIH propagates any of the host strains or phage, a sample will be sent to the investigator who developed the system or to an appropriate contractor, prior to distribution, for verification that the material is free from contamination and unchanged in phenotypic properties.

In distributing the certified HV2 and HV3 host-vector systems, NIH or its designee will (i) send out a complete description of the system; (ii) enumerate and describe the tests to be performed by the user in order to verify important phenotyic traits; (iii) remind the user that any modification of the system necessitates independent approval of the system by the NIH; and (iv) remind the user of responsibility for notifying ORDA of any discrepancies with the reported properties or any problems in the safe use of the system.

NIH may also distribute certified HV1 host-vector systems.

III. Containment Guidelines for Covered Experiments

Part III discusses experiments covered by the Guidelines. The reader must first consult Part I, where listings are given of prohibited and exempt experiments.

Containment guidelines for permissible experiments are given in Part III. Changes in these levels for specific experiments (or the assignment of levels to experiments not explicitly considered here) may not be instituted without the express approval of the Director, NIH. (See Sections IV-E-1-b-(1)-(a), IV-E-1-b-(1)-(b), IV-E-1-b-(2)-(b), IV-E-1-b-(2)-(c), and IV-E-1-b-(3)-(b).)

III-A. *Classification of Experiments Using the E. coli K-12 Host-Vector Systems.* Most recombinant DNA experiments currently being done employ *E. coli* K-12 host-vector systems. These are the systems for which we have the most experience and knowledge (i) regarding the effectiveness of biological containment provided by existing hosts and vectors and (ii) necessary for the construction of more effective biological barriers. We therefore consider DNA recombinants in *E. coli* K-12 before proceeding to other host-vector systems. The levels of biological containment for *E. coli* K-12 systems are designated EK1, EK2, and EK3 in ascending order.

It has been necessary, throughout this section, to use words and such terms are marked with footnote reference numbers. These footnotes (Part V) define more fully what the terms denote.

In the following classification of containment criteria for different kinds of recombinant DNAs, the stated levels of physical and biological containment are minimal for the experiments designated. The use of higher levels of biological containment (EK3>EK2>EK1) is encouraged if they are available and equally appropriate for the purposes of the experiment.

III-A-1. *Shotgun Experiments.* These experiments involve the production of recombinant DNAs between the vector and portions of the specified cellular source, preferably a partially purified fraction. Care should be taken either to preclude or eliminate contaminating microorganisms before isolating the DNA.

III-A-1-a. *Eukaryotic DNA Recombinants.*

III-A-1-a-(1). *Primates.* P2 physical containment+an EK2 host-vector. Any lowering of containment below these levels (i.e., for purified DNA or characterized clones) cannot be made solely by an institutional biosafety committee but requires NIH approval. (See Section IV-E-1-b-(3)-(e).)

III-A-1-a-(2). *Other Mammals.* P2 physical containment+an EK2 host-vector.

III-A-1-a0(3). *Birds.* P2 physical containment+an EK2 host-vector, or P3+EK1.

III-A-1-a-(4). *Cold-Blooded Vertebrates.* P2 physical containment+an EK1 host-vector or P1+EK2. If the eukaryote is known to produce a potent polypeptide toxin, [34] the containment shall be increased to P3+EK2.

III-A-1-a-(5). *Other Cold-Blooded Animals and Lower Eukaryotes.* This large class of eukaryotes is divided into two groups:

III-A-1-a-(5)-(a). Species that are known to produce a potent polypeptide toxin [34] that acts in vertebrates, or are known pathogens listed in Class 2, [1] or are known to carry such pathogens must use P3 physical containment+an EK2 host-vector. When the potent toxin is not a polypeptide and is likely not to be the product of closely linked eukaryote genes, containment may be reduced to P3+EK1 or P2+EK2. Species that produce potent toxins that affect invertebrates or plants but not vertebrates require P2+EK2 or P3+EK1. Any species that has a demonstrated capacity for carrying particular pathogenic microorganisms is included in this group, unless the organisms used as the source of DNA have been shown not to contain those agents, in which case they may be placed in the following group. [2A]

III-A-1-a-(5)-(b). The remainder of the species in this class including plant pathogenic or symbiotic fungi that do not produce potent toxins: P2 + EK1 or P1 + EK2. However, any insect in this group must be either (i) grown under laboratory conditions for at least 10 generations prior to its use as a source of DNA, or (ii) if caught in the wild, must be shown to be free of disease-causing microorganisms or must belong to a species that does not carry microorganisms causing disease in vertebrates or plants. [2A] If these conditions cannot be met, experiments must be done under P3 + EK1 or P2 + EK2 containment.

III-A-1-a-(6). *Plants.* P2 physical containment + an EK1 host-vector, or P1 + EK2. If the plant source makes a potent polypeptide toxin, [34] the containment must be raised to P3 physical containment + an EK2 host-vector. When the potent toxin is not a polypeptide and is likely not to be the product of closely linked plant genes, containment may be reduced to P3 + EK1 or P2 + EK2. [2A]

III-A-1-b. *Prokaryotic DNA Recombinants.*

III-A-1-b-(1). *Prokaryotes That Exchange Genetic Information [35] with E. Coli.* Those prokaryotes that exchange genetic information with *E. coli* by known physiological processes will be exempted from these Guidelines if they appear on the "list of exchangers" set forth in Appendix A (see Section I-E-4).

For those not on the list, the containment levels are P1 physical containment + an EK1 host-vector. In

fact, experiments in this category may be performed with any *E. coli* K-12 vector (e.g., conjugative plasmids). However, for prokaryotes that are classified [1] as Class 2, the containment levels are P2 + EK1.

III-A-I-b-(2). *Prokaryotes That Do Not Exchange Genetic Information with E. Coli.* P2 physical containment + an EK1 host-vector, or P1 + EK2, except for DNA from Class 2 agents, [1] which require P3 + EK2.

III-A-2. *Plasmids, Bacteriophages, and Other Viruses.* Recombinants formed between a vector and some other plasmid or virus DNA have in common the potential for acting as double vectors because of the replication functions in these DNAs. The containment conditions given below apply only to propagation of the DNA recombinants in *E. coli* K-12 hosts. They do not apply to other hosts in which the recombinants may be able to replicate as a result of functions provided by the DNA inserted into the EK vectors. These are considered under other host-vector systems.

III-A-2-a. *Viruses of Eukaryotes* (summary given in Table III).

III-A-2-a-(1). *DNA Viruses.*

III-A-2-a-(I)-(a). *Nontransforming viruses.*

III-A-2-a-(I)-(a)-(*1*). *Adeno-Associated Viruses, Minute Virus of Mice, Mouse Adenovirus (Strain FL), and Plant Viruses.* P1 physical containment + and EKI host-vector shall be used for DNA recombinants produced with (i) the whole viral genome, (ii) subgenomic DNA segments, or (iii) purified cDNA copies of viral mRNA. [37]

III-A-2-a-(I)-(a)-(*2*). *Hepatitis B.*

III-A-2-a-(I)-(a)-(*2*)-(*a*). P1 physical containment + an EK1 host-vector shall be used for purified subgenomic DNA segments. [38]

III-A-2-a-(1)-(a)-(*2*)-(*b*). P2 physical containment + an EK2 host-vector, or P3 + EK1, shall be used for DNA for recombinants produced with the whole viral genome or with subgenomic segments that have not been purified to the extent required in footnote 38.

III-A-2-a-(I)-(a)-(*2*)-(c). P2 physical containment + an EK1 host and a vector certified for use in an EK2 system, or P3 + EKI, shall be used for DNA recombinants derived from purified cDNA copies of viral mRNA. [37]

III-A-2-a-(1)-(a)-(*3*). *Other Nontransforming Members of Presently Classified Viral Families.* [*36*]

III-A-2-a-(1)-(a)-(*3*)-(*a*). PI physical containment + an EKI host-vector shall be used for (i) DNA recombinants produced with purified subgenomic DNA[38] segments or (ii) purified cDNA copies of viral mRNA. [37]

III-A-2-a-(1)-(a)-(*3*)-(*b*). PI physical containment + an EK1 host and a vector certified for use in an EK2 system shall be used for DNA recombinants produced with the whole viral genome or with subgenomic segments that have not been purified to the extent required in footnote 38.

III-A-2-a-(1)-(b). *Transforming Viruses.* [37A]

III-A-2-a-(1)-(b)-(*1*). *Herpes Saimiri, Herpes Ateles, and Epstein Barr Virus.* [*39*]

III-A-2-a-(1)-(b)-(*1*)-(*a*). PI physical containment + an EK1 host-vector shall be used for DNA recombinants produced with purified nontransforming subgenomic DNA segments. [38]

III-A-2-a-(I)-(b)-(*1*)-(*b*). P2 physical containment + an EK1 host and a vector certified for use in an EK2 system, or P3 + EK1, shall be used for (i) DNA recombinants produced with purified subgenomic DNA segments containing an entire transforming gene [38] or (ii) purified cDNA copies of viral mRNA. [37]

III-A-2-a-(I)-(b)-(*1*)-(c). P3 physical containment + an EKI host-vector, or P2 + EK2, shall be used for DNA recombinants produced with the whole viral genome or with subgenomic segments that have not been purified to the extent required in footnote 38.

III-A-2-a-(1)-(b)-(*2*). *Other Transforming Members of Presently Classified Viral Families.* [*36*]

III-A-2-a-(1)-(b)-(*2*)-(*a*). PI physical containment + an EK1 host-vector shall be used for DNA recombinants produced with purified nontransforming subgenomic DNA segments. [38]

III-a-2-a-(I)-(b)-(*2*)-(*b*). P2 physical containment + an EK1 host and a vector certified for use in an EK2 system, or P3 + EK1, shall be used for (i) DNA recombinants produced with the whole viral genome, (ii) subgenomic DNA segments containing an entire transforming gene, (iii) purified cDNA copies of viral mRNA, [37] or (iv) subgenomic segments that have not been purified to the extent required in footnote 38.

III-A-2-a-(2). *DNA Transcripts of RNA Viruses.*

III-A-2-a-(2)-(a). *Retroviruses.*

III-A-2-a-(2)-(a)-(*1*). *Gibbon Ape, Woolly Monkey, Feline Leukemia and Feline Sarcoma Viruses.* [*39*]

III-A-2-a-(2)-(a)-(*1*)-(*a*). P1 physical containment + an EK1 host-vector shall be used for DNA recombinants produced with purified nontransforming subgenomic DNA segments. [38]

III-A-2-a-(2)-(a)-(*1*)-(*b*). P2 physical containment + an EKI host and a vector certified for use in an EK2 system, or P3 + EKI, shall be used for DNA recombinants produced with purified subgenomic DNA segments [38] containing an entire transforming gene.

III-A-2-a-(2)-(a)-(*1*)-(c). P2 physical containment + an EK2 host-vector, or P3 + EK1, shall be used for DNA recombinants produced with (i) the whole viral genome, (ii) purified cDNA copies of viral mRNA, [37] or (iii) subgenomic segments that have not been purified to the extent required in footnote 38.

III-A-2-a-(2)-(a)-(*2*). *Other Members of the Family Retroviridiae.* [36]

III-A-2-a-(2)-(a)-(*2*)-(*a*). PI physical containment + an EK1 host-vector shall be used for DNA recombinants produced with purified nontransforming subgenomic DNA segments. [38]

III-A-2-a-(2)-(a)-(*2*)-(*b*). P2 physical containment + an EK1 host and a vector certified for use in an EK2 system, or P3 + EK1, shall be used for DNA recombinants produced with (i) subgenomic DNA segments containing an entire transforming gene, (ii) the whole viral genome, or (iii) purified cDNA copies of viral mRNA, [37] or (iv) subgenomic segments that have not been purified to the extent required in footnote 38.

III-A-2-a-(2)-(b). *Negative Strand RNA Viruses.* P1 physical containment + an EKI host-vector shall be used for DNA recombinants produced with (i) cDNA copies of the whole genome, (ii) subgenomic cDNA segments, or (iii) purified cDNA copies of viral mRNA. [37]

III-A-2-a-(2)-(c). *Plus-Strand RNA Viruses.*

III-A-2-a-(2)-(c)-(*1*). *Types 1 and 2 Sabin Poliovirus Vaccine Strains and Strain 17D (Theiler) of Yellow Fever Virus.* P1 physical containment + and EKI host-vector shall be used for DNA recombinants produced with (i) cDNA copies of the whole viral genome, (ii) subgenomic cDNA segments, or (iii) purified cDNA copies of viral mRNA. [37]

III-A-2-a-(2)-(c)-(*2*). *Other Plus Strand RNA Viruses Belonging to Presently Classified Viral Families.* [*36*]

Table III

Recommended Containment for Cloning of Viral DNA or cDNA in E. coli K-12 Host-Vector Systems
(See text for full details)

Virus class	Type of viral DNA segment to be cloned				
	Subgenomic[38]		Genomic		cDNA from viral mRNA[37]
	Nontransforming segment	Segment containing an entire transforming gene	Nonsegmented genome	Segmented genome	
DNA					
Nontransforming viruses					
AAV, MVM, Mouse Adeno (Strain FL)	P1 + EK1		P1 + EK1		P1 + EK1
Plant Viruses	P1 + EK1		P1 + EK1		P1 + EK1
Hepatitis B	P1 + EK1[38]		P2 + EK2 or P3 + EK1		P2 + EK1CV[40] or P3 + EK1
Other	P1 + EK1[38]		P1 + EK1CV[40]		P1 + EK1
Transforming Viruses					
Herpes Saimiri, H. Ateles and EBV[39]	P1 + EK1[38]	P2 + EK1CV[40] or P3 + EK1[38]	P2 + EK2 or P3 + EK1		P2 + EK1CV[40] or P3 + EK1
Other	P1 + EK1[38]	P2 + EK1CV[40] or P3 + EK1	P2 + EK1CV[40] or P3 + EK1		P2 + EK1CV[40] or P3 + EK1
RNA					
Retroviruses					
Gibbon Ape, Woolly Monkey FeLV and FeSV[39]	P1 + EK1[38]	P2 + EK1CV[40] or P3 + EK1[38]	P2 + EK2 or P3 + EK1		P2 + EK2 or P3 + EK1
Other	P1 + EK1[38]	P2 + EK1CV[40] or P3 + EK1	P2 + EK1CV[40] or P3 + EK1		P2 + EK1CV[40] or P3 + EK1

[39]

Table III

Recommended Containment for Cloning of Viral DNA or cDNA in *E. coli* K-12 Host-Vector Systems
(See text for full details)

Virus class	Type of viral DNA segment to be cloned				
	Subgenomic[38]		Genomic		cDNA from viral mRNA[37]
	Nontransforming segment	Segment containing an entire transforming gene	Nonsegmented genome	Segmented genome	
Negative-Strand RNA	P1 + EK1		P1 + EK1	P1 + EK1	P1 + EK1
Plus-Strand RNA					
Types 1 and 2 Sabin Polio, 17D Yellow Fever Vaccine Strains	P1 + EK1		P1 + EK1		P1 + EK1
Other	P1 + EK1[38]		P2 + EK1CV[40] or P3 + EK1		P2 + EK1CV[40] or P3 + EK1
Double-Stranded RNA	P1 + EK1			P1 + EK1	P1 + EK1
Plant Viruses + Viroids	P1 + EK1		P1 + EK1	P1 + EK1	P1 + EK1
Intracellular Viral DNA	See text	See text	See text		

II-A-2-a-(2)-(c)-(2)-(a). P1 physical containment + an EK1 host-vector shall be used for DNA recombinants produced with purified subgenomic cDNA segments.[38]

III-A-2-a-(2)-(c)-(2)-(b). P2 physical containment + an EK1 host and a vector certified for use in an EK2 system, or P3 + EK1, shall be used for DNA recombinants produced with (i) cDNA copies of the whole genome, or (ii) purified cDNA copies of viral mRNA.[37]

III-A-2-a-(2)-(d). *Double-Stranded Segmented RNA Viruses.* P1 physical containment + an EK1 host-vector shall be used for DNA recombinants produced with (i) mixtures of subgenomic cDNA segments, (ii) a specific subgenomic cDNA segment, or (iii) purified cDNA copies of viral mRNA.[37]

III-A-2-a-(2)-(e). *RNA Plant Viruses and Plant Viroids.* P1 physical containment + an EK1 host-vector shall be used for DNA recombinants produced with (i) cDNA copies of the whole viral genome, (ii) subgenomic cDNA segments, or (iii) purified cDNA copies of viral mRNA.[37]

III-A-2-a-(3). *Intracellular Viral DNA.* Physical and biological containment specified for shotgun experiments with eukaryotic cellular DNA [see Section III-A-(1)-(a)] shall be used for DNA recombinants produced with integrated viral DNA or viral genomes present in infected cells.

III-A-2-b. *Eukaryotic Organelle DNAs.* P2 physical containment + an EK1 host-vector, or P1 + EK2, for mitochondrial or chloroplast DNA from eukaryotes when the organelle DNA has been obtained from isolated organelles. Otherwise, the conditions given for shotgun experiments apply.

III-A-2-c. *Prokaryotic Plasmid and Phage DNAs.* The containment levels required for shotgun experiments with DNA from prokaryotes apply to their plasmids or phages.

III-A-3. *Lowering of Containment Levels for characterized or Purified DNA Preparations and Clones.* Many of the risks which might conceivably arise from some types of recombinant DNA experiments, particularly shotgun experiments, would result from the inadvertent cloning of a harmful sequence. Therefore, in case where the risk of inadvertently cloning the "wrong" DNA is reduced by prior enrichment for the desired piece, or in which a clone made from a random assortment of DNAs has been purified and the absence of harmful sequences established, the containment conditions for further work may be reduced. The following section outlines the mechanisms for such reductions.

III-A-3-a. *Purified DNA Other than Plasmids, Bacteriophages, and Other Viruses.* The formation of DNA recombinants from cellular DNAs that have been purified [41] and in which the absence of harmful sequences had been established [3] can be carried out under lower containment conditions than used for the corresponding shotgun experiment.[42] The containment may be decreased one step in physical containment (P4→P3; P3→P2; P2→P1) while maintianing the biological containment specified for the shotgun experiment, or one step in biological containment (EK3 → EK2; EK2 → EK1) while maintaining the specified physical containment. The institutional biosafety committee (IBC) must review such a reduction and the approval of the IBC must be secured before such a reduction may be put into effect. (See Section IV-D-3-b.) The IBC must notify the NIH Office of Recombinant DNA activities (ORDA) in writing of all such approvals within 30 days after they take place. IBC approval is sufficient for such a reduction except for (i) primate DNA, which also requires prior NIH approval (see Section III-A-1-a-(1)), or (ii) any lowering of containment under Section III-A-3-a to levels below P1 + EK1, which also requires prior NIH approval. (See Sections IV-D-1-c, IV-E-1-b-(3)-(e), and IV-E-1-b-(3)-(f).)

III-A-3-b. *Characterized Clones of DNA Recombinants.* When a cloned DNA recombinant has been rigorously characterized and the absence of harmful sequences has been established (3), experiments involving this recombinant DNA may be carried out under lower containment conditions, as described below.

III-A-3-b-(1). Institutional biosafety committees (IBCs) may give approval for a single-step reduction in physical or biological containment on receipt of evidence of characterization of a clone derived from a shotgun experiment and its probable freedom from harmful genes. (See Section IV-D-3-b.) The IBC must notify ORDA in writing of all such approvals within 30 days after they take place. IBC approval is sufficient for such a reduction except for (i) primate DNA, which requires prior NIH approval (see Section III-A-1-a-(1)), or (ii) any lowering of containment under Section III-A-3-b to levels below P1 + EK1, which also requires prior NIH Approval. (See Sections IV-D-1-c, IV-E-1-b-3-(e) and IV-E-1-b-(3)-(f).)

III-A-3-b-(2). Reduction of containment levels by more than one step, or cases involving primate DNA, or cases involving lowering of containment under Section III-A-3-b to levels below P1 + EK1, will require prior approval by NIH. (See Sections IV-E-1-b-(3)-(e), -(f) and -(g).)

III-B. *Experiments with Other Prokaryotic Host-Vectors.*

III-B-1. *HV1 Systems.* Host-vector systems which have been approved as HV1 systems may be used under P2 containment conditions for shotgun experiments with phages, plasmids, and DNA from nonpathogenic prokaryotes which do not produce polypeptide toxins.[34]

Other classes of recombinant DNA experiments with these HV1 systems will require prior approval and classification by NIH. Experiments with DNAs from eukaryotes (and their plasmids or viruses) will generally follow the criteria for the corresponding experiments with *E. coli* K-12 host-vectors if the major habitats of the given host-vector overlap those of *E. coli*. The habitats of other host-vector systems should also be considered in relation to containment.

II-B-2. *Return of DNA Segments to Non-HV1 Host of Origin.* Those prokaryotes tht exchange genetic information with *E. coli* by known physiological processes will be exempt from these Guidelines if they appear on the "list of exchangers" set forth in Appendix A (see Section I-E-4). For a prokaryote which can exchange genetic information [35] with *E. coli* under laboratory conditions but which is not on the list (Host A), the following type of experiment may be carried out under P-1 conditions without Host A having been approved as an HV1 host: DNA from Host A may be inserted into a vector and propagated in *E. coli* K-12 under P-1 conditions. Subsequently, this recombinant DNA may be returned to Host A by mobilization, transformation, or transduction and may then be propagated in Host A in any desired vector under P1 conditions.

For a prokaryote which does not exchange genetic information with *E. coli* (Host B), the following type of experiment may be carried out without Host B having been approved as an HV1 host: DNA from Host B may be inserted into a vector from a certified EK2 host-vector system and propagated in *E. coli* K-12 under the appropriate containment conditions [see Section III-A-1-b-(2)]. Subsequently, this recombinant DNA may be returned to Host B and propagated in Host B under P1 conditions.[43]

III-B-3. *Non-HV1 Systems.* Containment levels for other classes of experiments involving non-HV1 systems may be approved by the Director, NIH. (See Sections IV-E-1-b-(1)-(b), IV-E-1-b-(2)-(c) and IV-E-1-b-(3)-(b).)

III-C. *Experiments with Eukaryotic Host-Vectors.*

III-C-1. *Vertebrate Host-Vector Systems.*[44] (Summary given in Table IV).

III-C-1-a. *Polyoma Virus.*

III-C-1-a-(1). *Productive Virus-Cell Interactions.*

III-C-1-a-(1)-(a). Defective or whole polyoma virus genomes, with appropri-

ate helper, if necessary, can be used in P2 conditions to propagate DNA sequences:

III-C-1-a-(1)-(a)-(*1*). from bacteria of class 1 or class 2[1] or their phages or plasmids, except for those that produce potent polypeptide toxins; [34]

III-C-1-a-(1)-(a)-(*2*). from mice;

III-C-1-a-(1)-(a)-(*3*). from eukaryotic organisms that do not produce potent polypeptide toxins, [34] provided that the DNA segment is > 99% pure.

III-C-1-a-(1)-(b). Defective polyoma genomes, with appropriate helper, if necessary, can be used in P2 conditions for shotgun experiments to propagate DNA sequences from eukaryotic organisms that do not produce potent polypeptide toxins. [34]

III-C-1-a-(1)-(c). Whole virus genomes with appropriate helper, if necessary, can be used in P3 conditions for shotgun experiments to propagate DNA sequences from eukaryotic organisms that do not produce poten polypeptide toxins. [34]

III-C-1-a-(1)-(d). Experiments involving the use of defective polyoma virus genomes to propagate DNA sequences from eukaryotic viruses will be evaluated by NIH on a case-by-case basis [45] and will be conducted under the prescribed physical and biological containment conditions. (See Section IV-E-1-b-(3)-(c).)

III-C-1-a-(2). *Nonproductive Virus-Cell Interactions.* Defective or whole polyoma virus genomes can be used as vectors in P2 conditions when production of viral particles cannot occur (e.g., transformation of nonpermissive cells or propagation of an unconditionally defective recombinant genome in the absence of helper), provided the inserted DNA sequences are not derived from eukaryotic viruses. In the latter case, such experiments will be evaluated by NIH on a case-by-case basis [45] and will be conducted under the prescribed physical and biological containment conditions. (See Section IV-E-1-b-(3)-(c).)

III-C-1-b. *Simian Virus 40.*

III-C-1-b-(1). *Productive Virus-Cell Interactions.*

III-C-1-b-(1)-(a). SV40 DNA, rendered unconditionally defective by a deletion in an essential gene, with appropriate helper, can be used in P2 conditions to propagate DNA sequences from:

III-C-1-b-(1)-(a)-(*1*). bacteria of Class 1 or Class 2, -1] or their phages or plasmids, except for those that produce potent polypeptide toxins; [34]

III-C-1-b-(1)-(a)-(*2*). uninfected African green monkey kidney cell cultures.

III-C-1-b-(1)-(b). SV40 DNA, rendered unconditionally defective by a deletion in an essential gene, with an appropriate helper, can be used in P3 conditions to propagate DNA sequences from eukaryotic organisms that do not produce potent polypeptide toxins [34] (shotgun experiments or purified DNA).

III-C-1-b-(1)-(c). Experiments involving the use of defective SV40 genomes to propagate DNA sequences from eukaryotic viruses will be evaluated by NIH on a case-by-case basis [45] and will be conducted under the prescribed physical and biological containment conditions. (See Section IV-E-1-b-(3)-(c).)

III-C-1-b-(2). *Nonproductive Virus-Cell Interactions.* Defective or whole SV40 genomes can be used as vectors in P2 conditions when production of viral particles cannot occur (e.g., transformation of nonpermissive cells or propagation of an unconditionally defective recombinant genome in the absence of helper), provided the inserted DNA sequences are not derived from eukaryotic viruses. In the latter case, such experiments will be evaluated by NIH on a case-by-case basis -45] and will be conducted under the prescribed physical and biological containment conditions. (See Section IV-E-1-b-(3)-(c).)

III-C-1-c. *Human Adenoviruses 2 and 5.*

III-C-1-c-(1). *Productive Virus-Cell Interactions.*

III-C-1-c-(1)-(a). Human adenoviruses 2 and 5, rendered unconditionally defective by deletion of at least two essential genes, with appropriate helper, can be used in P3 conditions to propagate DNA sequences from:

III-C-1-c-(1)-(a)-(*1*). bacteria of Class 1 or Class 2[1] or their phages or plasmids except for those that produce potent polypeptide toxins; [34]

III-C-1-c-(1)-(a)-(*2*). eukaryotic organisms that do not produce potent polypeptide toxins[34] (shotgun experiments or purified DNA).

III-C-1-c-(1)-(b). Experiments involving the use of unconditionally defective human adenovirus 2 and 5 genomes to propagate DNA sequences from eukaryotic viruses will be evaluated by NIH on a case-by-case basis [45] and will be conducted under the prescribed physical and biological containment conditions. (See Section IV-E-1-b-(3)-(c).)

III-C-1-c-(2). *Nonproductive virus-cell interactions.* Defective or whole human adenovirus 2 and 5 genomes can be used as vectors in P2 conditions when production of viral particles cannot occur (e.g., transformation of nonpermissive cells or propagation of an unconditionally defective recombinant genome in the absence of helper), provided the inserted DNA sequences are not derived from eukaryotic viruses. In the latter case, such experiments will be evaluated by NIH on a case-by-case basis [45] and will be conducted under the prescribed physical and biological containment conditions. (See Section IV-E-1-b-(3)-(c).)

III-C-1-d. *Murine Adenovirus Strain FL.*

III-C-1-d-(1). *Productive Virus-Cell Interactions.*

III-C-1-d-(1)-(a). Unconditionally defective murine adenovirus strain FL genomes, with appropriate helper, can be used in P2 conditions to propagate DNA sequences from:

III-C-1-d-(1)-(a)-(*1*). bacteria of Class 1 or Class 2[1] or their phages or plasmids except for those that produce potent polypeptide toxins;[34]

III-C-1-d-(1)-(a)-(*2*). eukaryotic organisms that do not produce potent polypeptide toxins[34] (shotgun experiments or purified DNA).

III-C-1-d-(1)-(b). Experiments involving the use of whole murine adenovirus strain FL genomes to propagate DNA sequences from prokaryotic or eukaryotic organisms will be evaluated by NIH on a case-by-case basis[45] and will be conducted under the prescribed physical and biological containment conditions. (See Section IV-E-1-b-(3)-(c).)

III-C-1-d-(1)-(c). Experiments involving the use of unconditionally defective murine adenovirus strain FL genomes to propagate DNA sequences from eukaryotic viruses will be evaluated by NIH on a case-by-case basis[45] and will be conducted under the prescribed physical and biological containment conditions. (See Section IV-E-1-b-(3)-(c).)

III-C-1-d-(2). *Nonproductive Virus-Cell Interactions.* Defective or whole murine adenovirus strain FL genomes can be used as vectors in P2 conditions when production of viral particles cannot occur (e.g., transformation of nonpermissive cells or propagation of an unconditionally defective recombinant genome in the absence of helper), provided the inserted DNA sequences are not derived from eukaryotic viruses. In the latter case, such experiments will be evaluated by NIH on a case-by-case basis[45] and will be conducted under the prescribed physical and biological containment conditions. (See Section IV-E-1-b-(3)-(c).)

III-C-1-e. *All Other Potential Viral Vectors.*

III-C-1-e-(1). Experiments involving recombinant DNA molecules containing viral DNA segments consisting of 25% or less of the virus genome can be done:

III-C-1-e-(1)-(a). in P2 conditions when the recombinant DNA is to be integrated into the cell genome or is known to replicate as a plasmid in cells in culture, provided the additional DNA sequences are not derived from a eukaryotic virus. In the latter case, such experiments will be evaluated by NIH on a case-by-case basis [45]

and will be conducted under the prescribed physical and biological containment conditions. (See Section IV-E-1-b-(3)-(c).)

III-C-1-e-(1)-(b). Under physical and biological containment conditions to be determined by NIH[45] when a viral helper will be used to propagate DNA sequences from prokaryotic or eukaryotic organisms. (See Section IV-E-1-b-(3)-(c).)

III-C-1-e-(2). Experiments involving the use of other whole or defective virus genomes to propagate DNA sequences from prokaryotic or eukaryotic organisms (and viruses), or as vectors to transform nonpermissive cells, will be evaluated by NIH on a case-by-case basis[45] and will be conducted under the prescribed physical and biological containment conditions. (See Section IV-E-1-b-(3)-(c).)

NIH will also review on a case-by-case basis[45] all experiments involving the use of virus vectors in animals and will prescribe the physical and biological containment conditions appropriate for such studies. (See Section IV-E-1-b-(3)-(c).)

III-C-2. *Invertebrate Host-Vector Systems in Which Insect Viruses Are Used to Propagate Other DNA Segments.* As soon as information becomes available on the host range restrictions and on the infectivity, persistence, and integration of the viral DNA in vertebrate and invertebrate cells, experiments involving the use of insect viruses to propagate DNA sequences will be evaluated by NIH on a case-by-case basis[45] and will be conducted under the prescribed physical and biological containment conditions. (See Section IV-E-1-b-(3)-(c).)

III-C-3. *Plant Viral Host-Vector Systems.* The DNA plant viruses which could currently serve as vectors and cloning genes in plants and plant cell protoplasts are Cauliflower Mosaic Virus (CaMV) and its close relatives [2A] which have relaxed circular double-stranded DNA geromes with a molecular weight of 4.5×10^6, and Bean Golden Mosaic Virus (BGMV) and related viruses with small (10^6 daltons) single-stranded DNA genomes. CaMV is spread in nature by aphids, in which it survives for a few hours. Spontaneous mutants of CaMV which lack a factor essential for aphid transmission arise frequently. BGMV is spread in nature by whiteflies, and certain other single-stranded DNA plant viruses are transmitted by leafhoppers.

The DNA plant viruses have narrow host ranges and are relatively difficult to transmit mechanically to plants. For this reason, they are most unlikely to be accidentally transmitted from spillage of purified virus preparations.

When these viruses are used as vectors in intact plants, or propagative plant parts, the plants shall be grown under P1 conditions—that is, in either a limited access greenhouse or plant growth cabinet which is insect-restrictive, preferably with positive air pressure, [2A] and in which an insect fumigation regime is maintained. Soil, plant pots, and unwanted infected materials shall be removed from the greenhouse or cabinet in sealed insect-proof containers and sterilized. It is not necessary to sterilize run-off water from the infected plants, as this is not a plausible route for secondary infection. When the viruses are used as vectors in tissue cultures or in small plants in axenic cultures, no special containment is necessary. Infected plant materials which have to be removed from the greenhouse or cabinet for further research shall be maintained under insect-restrictive conditions. These measures provide an entirely adequate degree of containment. They are similar to those required in many countries for licensed handling of "exotic" plant viruses.

The CaMV strain used as a cloning vector shall be a mutant that lacks the aphid transmission factor.

The viruses or their DNA may also be useful as vectors to introduce genes into plant protoplasts. The fragility of plant protoplasts combined with the properties of the viruses provides adequate safety. Since no risk to the environment from the use of the DNA plant virus/protoplast system is envisaged, no special containment is necessary, except as described in the following paragraph.

Experiments involving the use of plant virus genomes to propagate DNA sequences from eukaryotic viruses will be evaluated by NIH on a case-by-case basis[45] and will be conducted under the prescribed physical and biological containment conditions. (See Section IV-E-1-b-(3)-(c).)

Table IV

Recommended Containment for Recombinant DNA Research Using Eukaryotic Viral Vectors
(See text for full details)

Vector DNA	Productive virus-cell interactions						Nonproductive virus-cell interactions[46]
	Type of DNA insert						
	Prokaryotic		Eukaryotic			Eukaryotic viral	
	Shotgun	Purified	Shotgun		Purified[47]		
			Natural host	Other			
1. Polyoma							
Intact Genome	P2	P2	P2	P3	P2	CBC*	P2
Deleted Genome	P2	P2	P2	P2	P2	CBC*	P2
2. SV40							
Intact Genome	—	—	—	—	—	—	P2
Deleted Genome	P2	P2	P2	P3	P3	CBC*	P2
3. Human Ad2+Ad5							
Deleted Genome	P3	P3	P3	P3	P3	CBC*	P2
4. Mouse Adenovirus (Strain FL)							
Intact Genome	CBC*	CBC*	CBC*	CBC*	CBC*	CBC*	P2
Deleted Genome	P2	P2	P2	P2	P2	CBC*	P2
5. Insect Viruses	CBC*	CBC*	CBC*	CBC*	CBC*	CBC*	—
6. Plant Viruses (CaMV and BGMV)	**	**	**	**	**	CBC*	—
7. All other potential Viral Vectors	CBC*	CBC*	CBC*	CBC*	CBC*	CBC*	CBC*

*CBC = case-by-case[45]
**See text

III-C-4. *Plant Host-Vector Systems Other than Viruses.* Organelle, plasmid, and chromosomal DNAs may be used as vectors. DNA recombinants formed between such vectors and host DNA, when propagated only in that host (or a closely related strain of the same species), are exempt from these Guidelines (see Section I-E). DNA recombinants formed between such vectors and DNA from cells other than the host species require P2 physical containment. The development of host-vector systems that exhibit a high level of biological containment, such as those using protoplasts or undifferentiated cells in culture, permit [2A] a decrease in the physical containment to P1.

Intact plants or propagative plant parts which cannot be grown in a standard P2 laboratory because of their large size may be grown under the P1 conditions described above in Section III-C-3, except that (i) sterilization of run-off water is required where this is a plausible route for secondary infection and (ii) the standard P2 practices are adopted for microbiological work.

III-C-5. *Fungal or Similar Lower Eukaryotic Host-Vector Systems.* The containment criteria for DNA recombinant experiments using these host-vectors most closely resemble those for prokaryotes, rather than those for the preceding eukaryotes, since the host cells usually exhibit a capacity for dissemination outside the laboratory that is similar to that for bacteria. Therefore, the procedures established for certification of HV systems other than *E. coli* K-12 (Section II-D-2) will also apply to these fungal or similar lower eukaryotic host-vector systems.

Once a HV1 system is approved by NIH, it may be used under P2 containment for shotgun experiments with phages, plasmids, and DNA from Class 1 prokaryotes[1] and lower eukaryotes that do not produce polypeptide toxins. [34] Other classes of recombinant DNA experiments with these HV1 systems will require prior approval and classification by NIH. (See Sections IV-E-1-b-(1)-(b), IV-E-1-b-(2)-(c) and IV-E-1-b-(3)-(b).) If HV2 or HV3 systems of this type are developed and approved by NIH, guidelines for their use in other types of recombinant DNA experiments will also be established.

In addition to the experiments described above, the following experiments may be carried out without the eukaryotic host (Host C) having been approved as an HV1 host: DNA from Host C may be inserted into a vector from a certified EK2 host-vector system and propagated in *E. coli* K-12 under the appropriate containment conditions [see Section III-A-1-(a)-(5)]. Subsequently, this recombinant DNA may be returned to Host C and propagated there under P1 conditions. [43]

Containment levels for other classes of experiments involving non-HV1 systems may be expressly approved by the Director, NIH. (See Sections IV-E-1-b-(1)-(b), IV-E-1-b-(2)-(c) and IV-E-1-b-(3)-(b).)

III-D. *Complementary DNAs.* Specific containment levels are given in Section III-A-a (see also last column of Table III) for complementary DNA (cDNA) or viral mRNA. For the other Sections of the Guidelines, where applicable, cDNAs synthesized *in vitro* are included within each of the above classifications. For example, cDNAs formed from cellular RNAs that are not purified and characterized are included under III-A-1, shotgun experiments; cDNAs formed from purified and characterized RNAs are included under III-A-3; etc.

Due to the possibility of nucleic acid contamination of enzyme preparations used in the preparation of cDNAs, the investigator must employ purified enzyme preparations that are free of viral nucleic acid.

III-E. *Synthetic DNAs.* If the synthetic DNA segment is likely to [2A] yield a potentially harmful polynucleotide or polypeptide (e.g., a toxin or a pharmacologically active agent), the containment conditions must be as stringent as would be used for propagating the natural DNA counterpart.

If the synthetic DNA sequence codes for a harmless product, [2A] it may be propagated at the same containment level as its purified natural DNA counterpart. For example, a synthetic DNA segment which corresponds to a non-harmful gene of birds, to be propagated in *E. coli* K-12, would require Ps physical containment plus an EK1 host-vector, or P1 + EK2.

If the synthetic DNA segment is not expressed *in vivo* as a polynucleotide or polypeptide product, the organisms containing the recombinant DNA molecules are exempt[4] from the Guidelines.

IV. Rules and Responsibilities

IV-A. *Policy.* Safety in activities involving recombinant DNA depends on the individual conducting them. The Guidelines cannot anticipate every possible situation. Motivation and good judgement are the key essentials to protection of health and the environment.

The Guidelines are intended to help the Institution, the Institutional Biosafety Committee (IBC), the Biological Safety Officer, and the Principal Investigator determine the safeguards that should be implemented. These Guidelines will never be complete or final, since all conceivable experiments involving recombinant DNA cannot be foreseen. Therefore, it is the responsibility of the Institution and those associated with it to adhere to the *purpose* of the Guidelines as well as to their specifics.

Each Institution (and the IBC acting on its behalf is responsible for ensuring that recombinant DNA activities comply with the Guidelines. General recognition of institutional authority and responsibility properly establishes accountability for safe conduct of the research at the local level.

The following roles and responsibilities constitute an administrative framework in which safety is an essential and integral part of research involving recombinant DNA molecules. Further clarifications and interpretations of roles and responsibilities will be issued by NIH as necessary.

IV-B. *General Applicability.* The Guidelines are applicable to all recombinant DNA research within the United States or its territories which is conducted at or sponsored by an Institution that receives any support for recombinant DNA research from NIH. This includes research performed by NIH directly.

An individual receiving support for research involving recombinant DNA must be associated with or sponsored by an Institution that can and does assume the responsibilities assigned in these Guidelines.

The Guidelines are also applicable to projects done abroad if they are supported by NIH funds. If the host country, however, has established rules for the conduct of recombinant DNA projects, then a certificate of compliance with those rules may be submitted to NIH in lieu of compliance with NIH Guidelines. NIH reserves the right to withhold funding if the safety practices to be employed abroad are not reasonably consistent with the NIH Guidelines.

IV-C. *General Definitions.* The following terms, which are used throughout the Guidelines, are defined as follows:

IV-C-1. "DNA" means deoxyribonucleic acid.

IV-C-2. "Recombinant DNA" or "recombinant DNA molecules" means either (i) molecules which are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or (ii) DNA molecules which result from the replication of a molecule described in (i) above.

IV-C-3. "Memorandum of Understanding and Agreement" or "MUA" is a document that (i) provides to NIH or other Federal funding agency an Institution's certification that the recombinant DNA research project complies with the NIH Guidelines and (ii) contains other essential data as required

in the Administrative Practices Supplement.

IV-C-4. "Institution" means any public or private entity (including Federal, State, and local government agencies).

IV-C-5. "Institutional Biosafety Committee" or "IBC" means a committee that (i) meets the requirements for membership specified in Section IV-D-2, and (ii) reviews, approves, and oversees projects in accordance with the responsibilities defined in Section IV-D-2 and -3.

IV-C-6. "NIH Office of Recombinant DNA Activities" or "ORDA" means the office within NIH with responsibility for (i) reviewing and coordinating all activities of NIH related to the Guidelines, and (ii) performing other duties as defined in Section IV-E—3.

IV-C-7. "Recombinant DNA Advisory Committee" or "RAC" means the public advisory committee that advises the Secretary, the Assistant Secretary for Health, and the Director of the National Institutes of Health concerning recombinant DNA research. The RAC shall be constituted as specified in Section IV-E-2.

IV-C-8. "Director, NIH" or "Director" means the Director of the National Institutes of Health and any other officer or employee of NIH to whom authority has been delegated.

IV-C-9 "Federal Interagency Advisory Committee on Recombinant DNA Research" means the committee established in October 1976 to advise the Secretary, HEW, the Assistant Secretary for Health, and the Director, NIH, on the coordination of those aspects of all Federal programs and activities which relate to recombinant DNA research.

IV-C-10. "Administrative Practice Supplement" or "APS" means a publication to accompany the NIH Guidelines specifying administrative procedures for use at NIH and at Institutions.

IV-C-11. "Laboratory Safety Monograph" or "LSM" means a publication to accompany the NIH Guidelines describing practices, equipment, and facilities in detail.

IV-D. *Responsibilities of the Institution*

IV-D-1. Each Institution conducting or sponsoring recombinant DNA research covered by these Guidelines is responsible for ensuring that the research is carried out in full conformity with the provisions of the Guidelines. In order to fulfill this responsibility, the Institution shall:

IV-D-1-a. Establish and implement policies that provide for the safe conduct of recombinant DNA research and that ensure compliance with the Guidelines. The Institution, as part of its general responsibilities for implementing the Guidelines, may establish additional procedures, as deemed necessary, to govern the Institution and its components in the discharge of its responsibilities under the Guidelines. This may include (i) statements formulated by the Institution for general implementation of the Guidelines and (ii) whatever additional precautionary steps the Institution may deem appropriate.

IV-D-1-b. Establish an Institutional Biosafety Committee (IBC) that meets the requirements set forth in Section IV-D-2 and carries out the functions detailed in Section IV-D-3.

IV-D-1-c. Submit, for each recombinant DNA project that meets with its approval, a Memorandum of Understanding and Agreement (MUA) to the funding agency for approval and registration. All projects, however, can proceed upon IBC approval (before submission of the MUA to the funding agency) except for the following, which require prior approval by NIH (or other funding agency designated by NIH for this purpose):

IV-D-1-c-(1). Projects for which containment levels are not specified by the Guidelines or NIH,

IV-D-1-c-(2). Projects requiring P4 containment,

IV-D-1-c-(3). Reductions of more than one step in containment levels (see Section III-A-3),

IV-D-1-c-(4). Reductions of containment level for projects involving primate DNA (see Section III-A-3),

IV-D-1-c-(5). Reductions of containment to levels below P1 + EK1 (see Section III-A-3),

IV-D-1-c-(6). The first project conducted in a facility at P3 containment, or

IV-D-1-c-(7). The first project conducted by an Institution.

NOTE: The MUA shall be submitted to the funding agency within 30 days of the IBC approval. If the funding agency does not routinely register recombinant DNA projects with NIH, the MUA must be submitted to NIH as well as to the funding agency. Authority to submit MUAs (or addenda) for which prior approval is not required may be delegated to the IBC chairperson. All MUAs that require NIH approval before the work can proceed shall be submitted to the NIH by the institutional official to whom the IBC is responsible.

IV-D-1-d. Take appropriate action to bring protocols into compliance when advised by NIH or other funding agency that IBC-approved projects do not conform to standards set forth in the Guidelines. This responsibility may be delegated to the IBC. (See Administrative Practices Supplement for further details).

IV-D-1-e. If the Institution is engaged in recombinant DNA research at the P3 or P4 containment level, appoint a Biological Safety Officer (BSO), who shall be a member of the IBC and carry out the duties specified in Section IV-D-4.

IV-D-1-f. Require that investigators responsible for research covered by these Guidelines comply with the provisions of Section IV-D-5, and assist investigators to do so.

IV-D-1-g. Ensure appropriate training for the IBC chairperson and members, the BSO, Principal Investigators (PIs), and laboratory staff regarding the Guidelines, their implementation, and laboratory safety. Responsibility for training IBC members may be carried out through the IBC chairperson. Responsibility for training laboratory staff may be carried out through the PI. The Institution is responsible for seeing that the PI has sufficient training, but may delegate this responsibility to the IBC.

IV-D-1-h. Determine the necessity, in connection with each project, for health surveillance of recombinant DNA research personnel, and conduct, if found appropriate, a health surveillance program for the project. [The Laboratory Safety Monograph (LSM) discusses various possible components of such a program—for example, records of agents handled, active investigation of relevant illnesses, and the maintenance of serial serum samples for monitoring serologic changes that may result from the employees' work experience. Certain medical conditions may place a laboratory worker at increased risk in any endeavor where infectious agents are handled. Examples given in the LSM include gastrointestinal disorders and treatment with steroids, immunosuppressive drugs, or antibiotics. Workers with such disorders or treatment should be evaluated to determine whether they should be engaged in research with potentially hazardous organisms during their treatment or illness.]

IV-D-1-i. Report within 30 days to ORDA any significant problems with and violations of the Guidelines and significant research-related accidents and illnesses, unless the institution determines that the PI or IBC has done so.

IV-D-2. *Membership and Procedure of the IBC.* The Institution shall establish an Institutional Biosafety Committee (IBC) meeting the following requirements:

IV-D-2-a. The IBC shall comprise no fewer than five members so selected that they collectively have experience and expertise in recombinant DNA technology and the capability to assess the safety of recombinant DNA research experiments and any potential risk to public health or the environment. At least two members (but not less than 20 percent of the mem-

bership of the committee) shall not be affiliated with the Institution (apart from their membership on the IBC) and shall represent the interest of the surrounding community with respect to health and protection of the environment. Members meet this requirement if, for example, they are officials of State or local public health or environmental protection agencies, members of other local governmental bodies, or persons active in medical, occupational health, or environmental concerns in the community. The Biological Safety Officer (BSO), mandatory when research is being conducted at the P3 and P4 levels, shall be a member (see Section IV-D-4).

IV-D-2-b. In order to ensure the professional competence necessary to review recombinant DNA activities, it is recomended that (i) the IBC include persons from disciplines relevant to recombinant DNA technology, biological safety, and engineering; (ii) the IBC include, or have available as consultants, persons knowledgeable in institutional commitments and policies, applicable law, standards of professional conduct and practice, community attitudes, and the environment; and (iii) at least one member be a nondoctoral person from a laboratory technical staff.

IV-D-2-c. The Institution shall identify the committee members by name in a report to the NIH Office of Recombinant DNA Activities (ORDA) and shall include relevant background information on each member in such form and at such times as ORDA may require. (See the Administrative Practices Supplement for further guidance.)

IV-D-2-d. No member of an IBC may be involved (except to provide information requested by the IBC) in the review or approval of a project in which he or she has been, or expects to be, engaged or has a direct financial interest.

IV-D-2-e. The Institution may establish procedures that the IBC will follow in its initial and continuing review of applications, proposals, and activities. (IBC review procedures are specified in section IV-D-3-a.)

IV-D-2-f. Central to implementation of the Guidelines is the review of proposed experiments by the IBC. The Institution shall submit, within 30 days of IBC approval, an MUA to NIH (ORDA), or shall otherwise register proposed experiments as specified under Sections IV-D-1-c, IV-D-1-d, and IV-F. In carrying out this responsibility, the Institution shall comply with instructions and procedures specified in the Administrative Practices Supplement.

IV-D-2-g. Institutions are encouraged to open IBC meetings to the public whenever possible, consistent with protection of privacy and proprietary interests.

IV-D-2-h. Upon request, the Institution shall make available to the public all minutes of IBC meetings and any documents submitted to or received from funding agencies which the latter are required to make available to the public (e.g., MUAs, reports of Guideline violations and significant research-related accidents, and agency directives to modify projects). If comments are made by members of the public on IBC actions, the Institution shall forward to NIH both the comments and the IBC's response.

IV-D-3. *Functions of the IBC.* On behalf of the Institution, the IBC is responsible for:

IV-D-3-a. Reviewing for compliance with the NIH Guidelines all recombinant DNA research to be conducted at or sponsored by the Institution, and approving those research projects that it finds are in conformity with the Guidelines. (See Administrative Practices Supplement, II-D, for prior NIH approval requirements.) This review shall include:

IV-D-3-a-(1). An independent assessment of the containment levels required by these Guidelines for the proposed research, and

IV-D-3-a-(2). An assessment of the facilities, procedures, and practices, and of the training and expertise of recombinant DNA personnel.

NOTE: See Laboratory Safety Monograph (pages 187-190) for suggested guidance in conducting this review.

IV-D-3-b. Authorizing the Principal Investigator (PI) to proceed with the project upon receipt of proper agency approval; or authorizing the PI to proceed without agency approval to initiate or change a project for which none of the exceptions under IV-D-1-c apply.

NOTE: Some examples of work that might ordinarily proceed without prior funding-agency approval are the initiation of a project at the P1 or P2 level (other than the first project at the institution). Other examples are significant changes in hosts or vectors, in the donor species or the nature of the DNA segment selected, or in the physical location of the experiments. Still others are single-step reductions in containment level for (i) experiments with DNA recombinants from cellular DNAs that have been purified and are judged to be free of harmful sequences (see Section III-A-3-a) and for (ii) clones that have been characterized and judged to be free of harmful sequences (see Section III-A-3-b). It should be clear, however, that the funding agency must be notified of IBC approvals even when prior agency approval is not required. See the Administrative Practices Supplement for further discussion.

IV-D-3-c. Reviewing periodically recombinant DNA research being conducted at the Institution, to insure that the requirements of the Guidelines are being fulfilled.

IV-D-3-d. Adopting emergency plans covering accidental spills and personnel contamination resulting from such research.

NOTE: Basic elements in developing specific procedures for dealing with major spills of potentially hazardous materials in the laboratory are detailed in the Laboratory Safety Monograph. Included are information and references on decontamination and emergency plans. NIH and the Center for Disease Control are available to provide consultation, and direct assistance if necessary, as posted in the LSM. The Institution shall cooperate with the State and local public health departments, reporting any significant research-related illness or accident that appears to be a hazard to the public health.

IV-D-3-e. Reporting within 30 days to the appropriate institutional officials and to the NIH Office of Recombinant DNA Activities (ORDA) any signficant problems with or violations of the Guidelines, and any significant research-related accidents or illnesses, unless the IBC determines that the PI has done so.

IV-D-3-f. Performing such other functions as may be delegated to the IBC under Section IV-D-1.

IV-D-4. *Biological Safety Officer.* The Institution shall appoint a BSO if it engages in recombinant DNA research at the P3 or P4 containment level. The officer shall be a member of the Institutional Biosafety Committee (IBC), and his or her duties shall include (but need not be limited to):

IV-D-4-a. Insuring through periodic inspections that laboratory standards are rigorously followed;

IV-D-4-b. Reporting to the IBC and the Institution all significant problems with and violations of the Guidelines and all significant research-related accidents and illnesses of which the BSO becomes aware, unless the BSO determines that the Principal Investigator (PI) has done so.

IV-D-4-c. Developing emergency plans for dealing with accidental spills and personnel contamination, and investigating recombinant DNA research laboratory accidents;

IV-D-4-d. Providing advice on laboratory security;

IV-D-4-e. Providing technical advice to the PI and the IBC on research safety procedures.

NOTE: See Laboratory Safety Monograph for additional information on the duties of the BSO.

IV-D-5. *Principal Investigator.* On behalf of the Institution, the PI is responsible for complying fully with the Guidelines in conducting any recombinant DNA research.

IV-D-5-a. *PI—General.* As part of this general responsibility, the PI shall:

IV-D-5-a-(1). Initiate or modify no recombinant DNA research subject to the Guidelines until that research, or the proposed modification thereof, has been approved by the Institutional Biosafety Committee (IBC) and has met all other requirements of the Guidelines and the Administrative Practices Supplement (APS), and make changes to conform if the NIH Office of Recombinant DNA Activities' (ORDA's) review so requires;

IV-D-5-a-(2). Report within 30 days to the IBC and NIH (ORDA) all significant problems with and violations of the Guidelines and all significant research-related accidents and illnesses;

IV-D-5-a-(3). Report to the IBC and to NIH (ORDA) new information bearing on the Guidelines;

IV-D-5-a-(4). Be adequately trained in good microbiological techniques;

IV-D-5-a-(5). Adhere to IBC-approved emergency plans for dealing with accidental spills and personnel contamination; and

IV-D-5-a-(6). Comply with shipping requirements for recombinant DNA molecules. (See Section II-C for shipping requirements, Laboratory Safety Monograph for technical recommendations, and the APS for administrative instructions and procedures. The requesting laboratory must be in compliance with the NIH Guidelines and under appropriate review by its IBC, and the sending investigator must maintain a record of all shipments of recombinant DNA materials.)

IV-D-5-b. *Submissions by the PI to NIH.* The PI shall:

IV-D-5-b-(1). Submit information to NIH (ORDA) in order to have new host-vector systems certified;

IV-D-5-b-(2). Petition NIH, with notice to the IBC, for exemptions to these Guidelines (see Sections I-E-4 and I-E-5 and, for additional information on procedures, the APS); and

IV-D-5-b-(3). Petition NIH, with concurrence of the IBC, for exceptions to the prohibitions under these Guidelines (see Section I-D and, for additional information on procedures, the APS).

IV-D-5-c. *Submissions by the PI to the IBC.* The PI shall:

IV-D-5-c-(1). Make the initial determination of the required levels of physical and biological containment in accordance with the Guidelines;

IV-D-5-c-(2). Select appropriate microbiological practices and laboratory techniques to be used in the research;

IV-D-5-c-(3). Submit the initial research protocol (and also subsequent changes—e.g., changes in the source of DNA or host-vector system, which require a new of revised Memorandum of Understanding and Agreement) to the IBC for review and approval or disapproval; and

IV-D-5-c-(4). Remain in communication with the IBC throughout the conduct of the project.

IV-D-5-d. *PI Responsibilities After Approval but Prior to Initiating the Research.* The PI is responsible for:

IV-D-5-d-(1). Making available to the laboratory staff copies of the approved protocols that describe the potential biohazards and the precautions to be taken;

IV-D-5-d-(2). Instructing and training staff in the practices and techniques required to ensure safety and in the procedures for dealing with accidents; and

IV-D-5-d-(3). Informing the staff of the reasons and provisions for any precautionary medical practices advised or requested, such as vaccinations or serum collection.

IV-D-5-e. *PI Responsibilities During the Conduct of the Approved Research.* The PI is responsible for:

IV-D-5-e-(1). Supervising the safety performance of the staff to ensure that the required safety practices and techniques are employed;

IV-D-5-e-(2). Investigating and reporting in writing to ORDA, the Biological Safety Officer (where applicable), and the IBC any significant problems pertaining to the operation and implementation of containment practices and procedures;

IV-D-5-e-(3). Correcting work errors conditions that may result in the release of recombinant DNA materials;

IV-D-5-e-(4). Ensuring the integrity of the physical containment (e.g., biological safety cabinets) and the biological containment (e.g., purity, and genotypic and phenotypic characteristics); and

IV-D-5-e-(5). *Publications.* PIs are urged to include, in all publications reporting on recombinant DNA research, a description of the physical and biological containment procedures employed.

IV-E. *Responsibilities of NIH.*

IV-E-1. *Director.* The Director, NIH, is responsible for (i) establishing the NIH Guidelines in recombinant DNA research, (ii) overseeing their implementation, and (iii) their final interpretation.

The Director has a number of responsibilities under the Guidelines that involve the NIH Office of Recombinant DNA Activities (ORDA) and the Recombinant DNA Advisory Committee (RAC). ORDA's responsibilities under the Guidelines are administrative. Advice from the RAC is primarily scientific and technical. In certain circumstances, there is specific opportunity for public comment, with published response, before final action.

IV-E-1-a. *General Responsibilities of the Director, NIH.* The responsibilities of the Director shall include the following:

IV-E-1-a-(1). Promulgating requirements as necessary to implement the Guidelines;

IV-E-1-a-(2). Establishing and maintaining the RAC to carry out the responsibilities set forth in Section IV-E-2. The RAC's membership is specified in its charter and in Section IV-E-2.

IV-E-1-a-(3). Establishing and maintaining ORDA to carry out the responsibilities defined in Section IV-E-3; and

IV-E-1-a-(4). Maintaining the Federal Interagency Advisory Committee on Recombinant DNA Research established by the Secretary, HEW, for advice on the coordination of all Federal programs and activities relating to recombinant DNA, including activities of the RAC.

IV-E-1-b. *Specific Responsibilities of the Director, NIH.* In carrying out the responsibilities set forth in this Section, the Director shall weigh each proposed action, through appropriate analysis and consultation, to determine that it complies with the Guidelines and presents no significant risk to health or the environment.

IV-E-1-b-(1). *The Director is responsible for the following major actions* (For these, the Director must seek the advice of the RAC and provide an opportunity for public and Federal agency comment. Specifically, the agenda of the RAC meeting citing the major actions will be published in the FEDERAL REGISTER at least 30 days before the meeting, and the Director will also publish the proposed actions in the FEDERAL REGISTER for comment at least 30 days before the meeting. In addition, the Director's proposed decision, at his discretion, may be published in the FEDERAL REGISTER for 30 days of comment before final action is taken. The Director's final decision, along with response to the comments, will be published in the FEDERAL REGISTER and the *Recombinant DNA Technical Bulletin.* The RAC and IBC chairpersons will be notified of this decision):

IV-E-1-b-(1)-(a). Changing containment levels for types of experiments that are specified in the Guidelines when a major action is involved;

IV-E-1-b-(1)-(b). Assigning containment levels for types of experiments that are not explicitly considered in the Guidelines when a major action is involved;

IV-E-1-b-(1)-(c). Certifying new host-vector systems, with the exception of minor modifications of already certified systems [The standards and procedures for certification are described in Section II-D-2-a. Minor modifications constitute, for example, those of minimal or no consequence to the properties relevant to containment. See the Administrative Prec-

tices Supplement (APS) for further information];

IV-E-1-b-(1)-(d). Promulgating and amending a list of classes of recombinant DNA molecules to be exempt from these Guidelines because they consist entirely of DNA segments from species that exchange DNA by known physiological processes, or otherwise do not present a significant risk to health or the environment (see Sections I-E-4 and -5 and the APS for further information);

IV-E-1-b-(1)-(e). Permitting exceptions to the prohibited experiments in the Guidelines, in order, for example, to allow risk-assessment studies; and

IV-E-1-b-(1)-(f). Adopting other changes in the Guidelines.

IV-E-1-b-(2). *The Director is also responsible for the following lesser actions.* (For these, the Director must seek the advice of the RAC. The Director's decision will be transmitted to the RAC and IBC chairpersons and published in the *Recombinant DNA Technical Bulletin*):

IV-E-1-b-(2)-(a). Interpreting and determining containment levels, upon request by ORDA;

IV-E-1-b-(2)-(b). Changing containment levels for experiments that are specified in the Guidelines (see Section III);

IV-E-1-b-(2)-(c). Assigning containment levels for experiments not explicitly considered in the Guidelines (see Section III); and

IV-E-1-b-(2)-(d). Designating certain class 2 agents as class 1 for the purpose of these Guidelines (see Footnote 1 and Appendix B).

IV-E-1-b-(3). *The Director is also responsible for the following actions* (The Director's decision will be transmitted to the RAC and IBC chairpersons and published in the *Recombinant DNA Technical Bulletin*):

IV-E-1-b-(3)-(a). Interpreting the Guidelines for experiments to which the Guidelines specifically assign containment levels;

IV-E-1-b-(3)-(b). Determining appropriate containment conditions for experiments according to case precedence developed under Section IV-E-1-b-(2)-(c).

IV-E-1-b-(3)-(c). Determining appropriate containment conditions upon case-by-case analysis of experiments explicitly considered in the Guidelines but for which no containment levels have been set (see Footnote 45 in Part V; Sections III-C-1-a through -e; and Sections III-C -2 and -3);

IV-E-1-b-(3)-(d). Authorizing, under procedures specified by the RAC, large-scale experiments (i.e., involving more than 10 liters of culture) for recombinant DNAs that are rigorously characterized and free of harmful sequences (see Footnote 3 and Section I-D-6);

IV-E-1-b-(3)-(e). Lowering containment levels one step for characterized clones involving primate DNA or for experiments using purified primate DNA (see Sections III-A-3-a and -b, and Footnotes 3 and 41);

IV-E-1-b-(3)-(f). Lowering containment levels for experiments involving other characterized clones or purified DNA below P1 + EK1 (see Sections III-A-3-a and -b, and Footnotes 3 and 41);

IV-E-1-b-(3)-(g). Lowering containment levels for characterized clones or purified DNA beyond one step (see Sections III-A-3-a and -b, and Footnotes 3 and 41);

IV-E-1-b-(3)-(h). Approving minor modifications of already certified host-vector systems. (The standards and procedures for such modifications are described in Section II-D-2-a); and

IV-E-1-b-(3)-(i). Decertifying already certified host-vector systems.

IV-E-1-b-(4). The Director shall conduct, support, and assist training programs in laboratory safety for Institutional Biosafety Committee members, Biological Safety Officers, Principal Investigators, and laboratory staff.

IV-E-1-b-(5). The Director, at the end of 36 months from the time these Guidelines are promulgated, will report on the Guidelines, their administration, and the potential risks and benefits of this research. In doing so, the Director will consult with the RAC and the Federal Interagency Committee. Public comment will be solicited on the draft report and taken into account in transmitting the final report to the Assistant Secretary for Health and the Secretary, HEW.

IV-E-2. *Recombinant Advisory Committee.* The NIH Recombinant DNA Advisory Committee (RAC) is responsible for carrying out specified functions cited below as well as others assigned under its charter or by the Secretary, HEW, the Assistant Secretary for Health, and the Director, NIH.

The members of the committee shall be chosen to provide, collectively, expertise in scientific fields relevant to recombinant DNA technology and biological safety—e.g., microbiology, molecular biology, virology, genetics, epidemiology, infectious dieseases, the biology of enteric organisms, botany, plant pathology, ecology, and tissue culture. At least 20 percent of the members shall be persons knowledgeable in applicable law, standards of professional conduct and practice, public attitudes, the environment, public health, occupational health, or related fields. Representatives from Federal agencies shall serve as nonvoting members. Nominations for the RAC may be submitted to the NIH Office of Recombinant DNA Activities.

All meetings of the RAC will be announced in the FEDERAL REGISTER, including tentative agenda items, 30 days in advance of the meeting, with final agendas (if modified) available at least 72 hours before the meeting. No item defined as a major action under Section IV-E-1-b-(1) may be added to an agenda after it appears in the FEDERAL REGISTER.

IV-E-2-a. *The RAC shall be responsible for advising the Director, NIH, on the actions listed in Section IV-E-1-b-(1) and -(2).*

IV-E-3. *The Office of Recombinant DNA Activities.* ORDA shall serve as a focal point for information on recombinant DNA activities and provide advice to all within and outside NIH, including Institutions, Biological Safety Committees, Principal Investigators, Federal agencies, State and local governments, and institutions in the private sector. ORDA shall carry out such other functions as may be delegated to it by the Director, NIH, including those authorities described in Section IV-E-1-b-(3). In addition, ORDA shall be responsible for the following:

IV-E-3-a. Review and approval of Institutional Biosafety Committee (IBC) membership;

IV-E-3-b. Registration of recombinant DNA projects; and

IV-E-3-c. Review of Memoranda of Understanding and Agreement (MUAs), and approval of those that conform to the Guidelines. In so doing, ORDA shall:

IV-E-3-c-(1). Conduct an independent evaluation of the containment levels required for the research covered by these Guidelines;

IV-E-3-c-(2). Determine whether the physical and biological containment levels approved by the IBC are in accordance with the requirement of the Guidelines;

IV-E-3-c-(3). Notify Institutions and the IBC chairperson in a timely fashion when MUAs (including changes in ongoing projects) do not conform to the Guidelines, and inform them of corrective measures to be taken;

IV-E-3-c-(4). Publish in the FEDERAL REGISTER:

IV-E-c-(4)-(a). Announcements of Recombinant DNA Advisory Committee (RAC) meetings and agendas 30 days in advance, with publication of the Director's proposed decision for 30 days of public and Federal agency comment followed by a published response, on any action listed in Section IV-E-1-b-(1); and

IV-E-3-c-(4)-(b). Announcements of RAC meetings and agendas 30 days in advance on any action listed in Section IV-E-1-b-(2).

NOTE.—If the agenda for an RAC meeting is modified, ORDA shall make the revised agenda available to anyone, upon request, at least 72 hours in advance of the meeting.

IV-E-3-c-(5). Publish the *Recombinant DNA Technical Bulletin*; and

IV-E-3-c-(6). Serve as executive secretary to the RAC.

IV-E-4. *Other NIH Components.* Other NIH components shall be responsible for:

IV-E-4-a. Awarding no grant or contract involving recombinant DNA techniques unless a properly executed MUA has been received;

IV-E-4-b. Certifying P4 facilities, inspecting them periodically and inspection other recombinant DNA facilities as deemed necessary; and

IV-E-4-c. Announcing and distributing certified HV2 and HV3 host-vector systems (see Section II-E-3).

(See Administrative Practices Supplement for additional information on the administrative procedures of ORDA and other NIH components.)

IV-F. *Registration*

IV-F-1. *Required Registration.* Institutions receiving NIH funds for recombinant DNA projects shall inform NIH of all recombinant DNA projects at the institution. A non-NIH project, after approval by the Institutional Biosafety Committee, shall be registered with NIH within 30 days of initiation. Applications for NIH projects must be accompanied by a Memorandum of Understanding and Agreement (MUA).

For information on MUAs or equivalent documents that must be submitted for registration of recombinant DNA projects, see the Administrative Practices Supplement (APS).

IV-F-2. *Federal Agency Registration.* Institutions at which recombinant DNA research projects funded by other Federal agencies are conducted need not register such projects with NIH when the Federal agency maintains a registry and provides such information to NIH. Registration of non-NIH-funded research with the NIH Office of Recombinant DNA Activities (ORDA) is described in the APS. (The information required is similar to that in an MUA for NIH-supported research.)

IV-F-3. *Voluntary Registration and Certification.* Any institution that is not required to comply with the Guidelines may nevertheless register recombinant DNA research projects with NIH by submitting the appropriate information to ORDA. NIH will accept requests for certification of host-vector systems proposed by the institition. The submitter must agree to abide by the physical and biological containment standards of the NIH Guidelines.

IV-F-4. *Disclosure of Information.* Institutions are reminded that they should consider applying for a patent before submitting information to DHEW which they regard as potentially proprietary. (Provisions for protection of proprietary information as permitted under current DHEW authorities will be proposed as a future supplement to these Guidelines.)

IV-G. *Compliance.* As a condition for NIH funding of recombinant DNA research, Instititions must ensure that such research conducted at or sponsored by the Instititon, irrespective of the source of funding, shall comply with these Guidelines. The policies on noncompliance are as follows:

IV-G-1. All NIH-funded projects involving recombinant DNA techniques must comply with the NIH Guidelines. Noncompliance may result in (i) suspension, limitation, or termination of financial assistance for such projects and of NIH funds for other recombinant DNA research at the Institution, or (ii) a requirement for prior NIH approval of any or all recombinant DNA projects at the Institution.

IV-G-2. All non-NIH-funded projects involving recombinant DNA techniques conducted at or sponsored by an Institution that receives NIH funds for projects involving such techniques must comply with the NIH Guidelines. Noncompliance may result in (i) suspension, limitation, or termination of NIH funds for recombinant DNA research at the Institution, or (ii) a requirement for prior NIH approval of any or all recombinant DNA projects at the Institution.

IV-G-3. Information concerning noncompliance with the Guidelines may be brought forward by any person. It should be delivered to both NIH (ORDA) and the relevant Institution. The Institution, generally through the IBC, shall take appropriate action. The Institution shall forward a complete report of the incident to ORDA, recommending any further action indicated.

IV-G-4. In cases where NIH proposes to suspend, limit, or terminate financial assistance because of noncompliance with the Guidelines, applicable DHEW and Public Health Service procedures shall govern.

V. FOOTNOTES AND REFERENCES

1. The reference to organisms as Class 1, 2, 3, 4, or 5 refers to the classification in the publication *Classification of Etiologic Agents on the Basis of Hazard*, 4th Edition, July 1974; U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Office of Biosafety, Atlanta, Georgia 30333. The list of organisms in each class, as given in this publication, is reprinted in Appendix B to these Guidelines.

The Director, NIH, with advice of the Recombinant DNA Advisory Committee, may designate certain of the agents which are listed as Class 2 in the *Classification of Etiologic Agents on the Basis of Hazard*, 4th Edition, July 1974, as Class 1 agents for the purposes of these Guidelines (see Section IV-E-1-b-(2)-(d)). An updated list of such agents may be obtained from the Office of Recombinant DNA Activities (ORDA), National Institutes of Health, Bethesda, Maryland 20014.

The entire *Classification of Etiologic Agents on the Basis of Hazard* is in the process of revision.

One exception to the prohibition of formation of recombinant DNAs derived from Class 3, 4, or 5 agents is that the formation of recombinant DNAs derived from Vesicular Stomatitis Virus (VSV) is not prohibited. The reason for this is explained in the "Decision Document" accompanying the proposed revised guidelines published in the FEDERAL REGISTER on July 28, 1978. However, as noted in Appendix B, a permit from the U.S. Department of Agriculture is required for the import or interstate transport of VSV. This can be obtained form USDA-APHIS, Veterinary Service, Federal Building, Hyattsville, Maryland 20782.

2A. In Parts I and III of the Guidelines, there are a number of places where judgments are to be made. These include: "cells known to be infected with such agents" (Section I-D-1); "toxins potent for vertebrates" (Section I-D-2); "beyond that which occurs by natural genetic exchange" (Section I-D-3); "known to acquire it naturally" (Section I-D-5); "known to produce a potent polypeptide toxin * * * or known to carry such pathogens * * * not likely to be a product of closely linked eukaryote genes * * * shown not to contain such agents" (Section III-A-1-a-(5)-(a)); "shown to be free of disease causing microorganisms" (Section III-A-1-a-(5)-(b)); "close relatives" (Section III-C-3); and "produce a potent polypeptide toxin" (Footnote 34).

In all these cases the principal investigator is to make the initial judgment on these matters as part of his responsibility to "make the initial determination of the required levels of physical and biological containment in accordance with the Guidelines" (Section IV-D-7-a). In all these cases, this judgment is to be reviewed and approved by the Institutional Biosafety Committee as part of its rsponsibility to make "an independent assessment of the containment levels required by these Guidelines for the proposed research" (Section IV-D-3-a-(1)). If the IBC wishes, any specific cases may be referred to the NIH Office of Recombinant DNA Activities as part of ORDA's functions to "provide advice to all within and outside NIH" (Section IV-E-3), and ORDA may request advice from the Recombinant DNA Advisory Committee as part of the RAC's responsibility for "interesting and determining containment levels upon request by ORDA" (Section IV-E-1-b-(2)-(a)).

3. The following types of data should be considered in determining whether DNA recombinants are "characterized" and the absence of harmful sequences has been established: (a) The absence of potentially harmful genes (e.g., sequences contained in indigenous tumor viruses or sequences that code for toxins, invasins, virulence factors, etc., that might potentiate the pathogenicity or communicability of the vector and/or the host or be detrimental to humans, animals, or plants); (b) the types(s) of genetic information on the cloned segment and the nature of transcriptional and translation gene products specified; (c) the relationship

between the recovered and desired segment (e.g., hybridization and restriction endonuclease fragmentation analysis where applicable); (d) the genetic stability of the cloned fragment; and (e) any alterations in the biological properties of the vector and host.

4. In Section I-E, "exemptions" from the Guidelines are discussed. Such experiments are not covered by the Guidelines and need not be registered with NIH. In Section I-D on "prohibitions," the possibility of "exceptions" is discussed. An "exception" means that an experiment may be expressly released from a prohibition. At that time it will be assigned appropriate

5. Care should be taken to inactivate recombinant DNA before disposal. Procedures for inactivating DNA can be found in the "Laboratory Safety Monograph: A Supplement to the NIH Guidelines for Recombinant DNA Research."

6. *Laboratory Safety at the Center for Disease Control* (Sept. 1974). U.S. Department of Health, Education and Welfare Publication No. CDC 75-8118.

7. *Classification of Etiologic Agents on the Basis of Hazard.* (4th Edition, July 1974). U.S. Department of Health, Education and Welfare. Public Health Service. Center for Disease Control, Office of Biosafety, Atlanta, Georgia 30333.

8. *National Cancer Institute Safety Standards for Research Involving Oncogenic Viruses* (Oct. 1974). U.S. Department of Health, Education and Welfare Publication No. (NIH) 75-790.

9. *National Institutes of Health Biohazards Safety Guide* (1974). U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health. U.S. Government Printing Office, Stock No. 1740-00383.

10. *Biohazards in Biological Research* (1973). A. Hellman, M. N. Oxman, and R. Pollack (ed.) Cold Spring Harbor Laboratory.

11. *Handbook of Laboratory Safety* (1971). Second Edition. N. V. Steere (ed.). The Chemical Rubber Co., Cleveland.

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14. *The Prevention of Laboratory Acquired Infection* (1974). C. H. Collins, E. G. Hartley, and R. Pilsworth. Public Health Laboratory Service, Monograph Series No. 6.

15. Chatigny, M. A. (1961). *Protection Against Infection in the Microbiological Laboratory: Devices and Procedures.* In W. W. Umbreit (ed.). Advances in Applied Microbiology. Academic Press, New York, N.Y. 3:131-192.

16. *Design Criteria for Viral Oncology Research Facilities* (1975). U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, DHEW Publication No. (NIH) 75-891.

17. Kuehne, R. W. (1973). *Biological Containment Facility for Studying Infectious Disease.* Appl. Microbiol. 26-239-243.

18. Runkle, R. S., and G. B. Phillips (1969). *Microbial Containment Control Facilities.* Van Nostrand Reinhold, New York.

19. Chatigny, M. A., and D. I. Clinger (1969). *Contamination Control in Aerobiology.* In R. L. Dimmick and A. B. Akers (eds.). An Introduction to Experimental Aerobiology. John Wiley & Sons, New York, pp. 194-263.

19A Horsfall, F. L., Jr., and J. H. Baner (1940). *Individual Isolation of Infected Animals in a Single Room.* J. Bact. *40*, 569-580.

20. Biological safety cabinets referred to in this section are classified as *Class I, Class II,* or *Class III* cabinets. A *Class I* is a ventilated cabinet for personnel protection having an inward flow of air away from the operator. The exhaust air from this cabinet is filtered through a high-efficiency particulate air (HEPA) filter. This cabinet is used in three operational modes: (1) With a full-width open front, (2) with an installed front closure panel (having four 8-inch diameter openings) without gloves, and (3) with an installed front closure panel equipped with arm-length rubber gloves. The face velocity of the inward flow of air through the full-width open front is 75 feet per minute or greater. A *Class II* cabinet is a ventilated cabinet for personnel and product protection having an open front with inward air flow for personnel protection, and HEPA filtered mass recirculated air flow for product protection. The cabinet exhaust air is filtered through a HEPA filter. The face velocity of the inward flow of air through the full-width open front is 75 feet per minute or greater. Design and performance specifications for *Class II* cabinets have been adopted by the National Sanitation Foundation, Ann Arbor, Michigan. A *Class III* cabinet is a closed-front ventilated cabinet of gas-tight construction which provides the highest level of personnel protection of all biohazard safety cabinets. The interior of the cabinet is protected from contaminants exterior to the cabinet. The cabinet is fitted with arm-length rubber gloves and is operated under a negative pressure of at least 0.5 inches water gauge. All supply air is filtered through HEPA filters. Exhaust air is filtered through two HEPA filters or one HEPA filter and incinerator before being discharged to the outside environment.

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33. Leder, P., D. Tiemeier and L. Enquist (1977). *EK2 Derivatives of Bacteriophage Lambda Useful in the Cloning of DNA from Higher Organisms: The gt WES System.* Science *196*. 175-177.

33A. Skalka, A. (1978). *Current Status of Coliphage EK2 Vectors.* Gene *3*, 29-35.

33B. Szybalski, W., A. Skalka, S. Gottesman, A. Campbell, and D. Botstein (1978). *Standardized Laboratory Tests for EK2 Certification.* Gene *3*, 36-38.

34. We are specifically concerned with the remote possibility that potent toxins could be produced by acquiring a single gene or cluster of genes. See also footnote 2A.

35. Defined as observable under optimal laboratory conditions by transformation, transduction, phage infection, and/or conjugation with transfer of phage, plasmid, and/or chromosomal genetic information. Note that this definition of exchange may be less stringent than that applied to exempt organisms under Section I-E-4.

36. As classified in the Second Report of the International Committee on Taxonomy of Viruses: Classification and Nomenclature of Viruses, Frank Penner, Ed. Intervirology 7 (19-115) 1976. (As noted in the Prohibition Section, the use of viruses classified[1] as Class 3, 4, or 5, other than VSV, is prohibited.)

37. The cDNA copy of the viral mRNA must be >99% pure; otherwise as for shotgun experiments with eukaryotic cellular DNA.

37A. For the purpose of these Guidelines, viruses of the families *Papovaviridae, Adenoviridae,* and *Herpetoviridae* (36) should be considered as "transforming" viruses. While only certain of these viruses have been associated with cell transformation *in vivo* or *in vitro,* it seems prudent to consider all members to be potentially capable of transformation. In addition, those viruses of the family *Poxviridae* that produce proliferative responses—i.e., myxoma, rabbit and squirrel fibroma, and Yaba viruses—should be considered as "transforming."

38. >99% pure (i.e., less than 1% of the DNA consists of intact viral genomes); otherwise as for whole genomes.

39. The viruses have been classified by NCI as "moderate-risk oncogenic viruses." See "Laboratory Safety Monograph—A Supplement to the NIH Guidelines for Recombinant DNA Research" for recommendations on handling the viruses themselves.

40. EK1CV means the use of an EK1 host and a vector certified for use in an EK2 system.

41. The DNA preparation is defined as "purified" if the desired DNA represents at least 99% (w/w) of the total DNA in the preparation, provided that it was verified by more than one procedure.

42. The lowering of the containment level when this degree of purification has been obtained is based on the fact that the total number of clones that must be examined to obtain the desired clone is markedly reduced. Thus, the probability of cloning a harmful gene could, for example, be reduced by more than 10-fold when a nonrepetitive gene from mammals was being sought. Furthermore, the level of purity specified here makes it easier to establish that the desired DNA does not contain harmful genes.

43. This is not permitted, of course, if it falls under any of the Prohibitions of Section I-D. Of particular concern here is prohibition I-D-5, i.e., "Deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire it naturally, if such acquisition could compromise the use of a drug to control disease agents in human or veterinary medicine or agriculture."

44. Because this work will be done almost exclusively in tissue culture cells, which have no capacity for propagation outside the laboratory, the primary focus for containment is the vector. It should be pointed out that risk of laboratory-acquired infection as a consequence of tissue culture manipulation is very low. Given good microbiological practices, the most likely mode of escape of recombinant DNAs from a physically contained laboratory is carriage by an infected human. Thus the vector with an inserted DNA segment should have little or no ability to replicate or spread in humans.

For use as a vector in a vertebrate host cell system, an animal viral DNA molecule should display the following properties:

(i) It should not consist of the whole genome of any agent that is infectious for humans or that replicates to a significant extent in human cells in tissue culture. If the recombinant molecule is used to transform nonpermissive cells (i.e., cells which do not produce infectious virus particles), this is not a requirement.

(ii) It should be derived from a virus whose epidemiological behavior and host range are well understood.

(iii) In permissive cells, it should be defective when carrying an inserted DNA segment (i.e., propagation of the recombinant DNA as a virus must be dependent upon the presence of a complementing helper genome). In almost all cases this condition would be achieved automatically by the manipulations used to construct and propagate the recombinants. In addition, the amount of DNA encapsidated in the particles of most animal viruses is defined within fairly close limits. The insertion of sizable foreign DNA sequences, therefore, generally demands a compensatory deletion of viral sequences. It may be possible to introduce very short insertions (50-100 base pairs) without rendering the viral vector defective. In such a situation, the requirement that the viral vector be defective is not necessary, except in those cases in which the inserted DNA encodes a biologically active polypeptide.

It is desired but not required that the functional anatomy of the vector be known—that is, there should be a clear idea of the location within the molecule of:

(i) The sites at which DNA synthesis originates and terminates,

(ii) The sites that are cleaved by restriction endonucleases, and

(iii) The template regions for the major gene product.

If possible the helper virus genome should: (i) Be integrated into the genome of a stable line of host cells (a situation that would effectively limit the growth of the vector recombinant to such cell lines) or

(ii) Consist of a defective genome, or an appropriate conditional lethal mutant virus, making vector and helper dependent upon each other for propagation.

However, neither of these stipulations is a requirement.

45. Review by NIH on a case-by-case basis means that NIH must review and set appropriate containment conditions before the work may be undertaken. NIH actions in such case-by-case reviews will be published in the *Recombinant DNA Technical Bulletin.*

46. Provided the inserted DNA sequences are not derived from eukaryotic viruses. In the latter case, such experiments will be evaluated on a case-by-case basis.

47. >99% pure; otherwise as for shotgun experiments.

Appendix A

Section I-E-4 states that exempt from these Guidelines are "certain specified recombinant DNA molecules that consist entirely of DNA segments from different species that exchange DNA by known physiological processes, though one or more of the segments may be a synthetic equivalent. A list of such exchangers will be prepared and periodically revised by the Director, NIH, with advice of the Recombinant DNA Advisory Committee, after appropriate notice and opportunity for public comment (see Section IV-E-1-b-(1)-(d).) Certain classes are exempt as of publication of these Revised Guidelines. The list is in Appendix A."

Under exemption I-E-4 of these revised Guidelines are recombinant DNA molecules that are (1) composed entirely of DNA segments from one or more of the organisms of the following classes, and (2) to be propagated in any of the organisms listed below. (Classification of *Bergey's Manual of Determinative Bacteriology,* eighth edition. R. E. Buchanan and N. E. Gibbons, editors. Williams and Wilkins Company: Baltimore, 1974.)

1. Genus *Escherichia*
2. Genus *Shigella*
3. Genus *Salmonella* (including *Arizona*)
4. Genus *Enterobacter*
5. Genus *Citrobacter* (including *Levinea*)
6. Genus *Klebsiella*
7. *Erwinia amylovora*
8. *Pseudomonas aeruginosa*
9. *Serratia marcescens*

Appendix B

Classification of Microorganisms on the Basis of Hazard

I. Classification of Etiologic Agents on the Basis of Hazard (1)

A. *Class 1 Agents*

All bacterial, parasitic, fungal, viral, rickettsial, and chlamydial agents not included in higher classes.

B. *Class 2 Agents*

1. *Bacterial Agents*

Actinobacillus—all species except *A. mallei,* which is in Class 3
Arizona hinshawii—all serotypes
Bacillus anthracis
Bordetella—all species
Borrelia recurrentis, B. vincenti
Clostridium botulinum, Cl. chauvoei, Cl. haemolyticum, Cl. histolyticum, Cl. novyi, Cl. septicum, Cl. tetani
Corynebacterium diptheriae, C. equi, C. haemolyticum, C. pseudotuberculosis, C. pyogenes, C. renale
Diplococcus (Streptococcus) pneumoniae
Erysipelothrix insidiosa
Escherichia coli—all enteropathogenic serotypes
Haemophilus ducreyi, H. influenzae
Herellae vaginicola
Klebsiella—all species and all serotypes
Leptospira interrogans—all serotypes
Listeria—all species
Mima polymorpha
Moraxella—all species
Mycobacteria—all species except those listed in Class 3
Mycoplasma—all species except *Mycoplasma mycoides* and *Mycoplasma agalactiae,* which are in Class 5
Neisseria gonorrhoeae, N. meningitidis
Pasteurella—all species except those listed in Class 3
Salmonella—all species and all serotypes
Shigella—all species and all serotypes
Sphaerophorus necrophorus
Staphylococcus aureus
Streptobacillus moniliformis
Streptococcus pyogenes
Treponema carateum, T. pallidum, and T. pertenue
Vibrio fetus, V. comma, including biotype El Tor, and *V. parahemolyticus*

2. *Fungal Agents*

[1] *Actinomycetes* (including *Nocardia* species and *Actinomyces species and Arachnia propionica*)
Blastomyces dermatitidis
Cryptococcus neoformans
Paracoccidioides brasiliensis

3. *Parasitic Agents*

Endamoeba histolytica
Leishmania sp.
Waegleria gruberi
Toxoplasma gondii
Toxocara canis
Trichinella spiralis
Trypanosoma cruzi

4. *Viral, Rickettsial, and Chlamydial Agents*

Adenoviruses—human—all types
Cache Valley virus

[1] Since the publication of the classification in 1974 [1], the *Actinomycetes* have been reclassified as bacterial rather than fungal agents.

Coxsackie A and B viruses
Cytomegaloviruses
Echoviruses—all types
Encephalomyocarditis virus (EMC)
Flanders virus
Hart Park virus
Hepatitis-associated antigen material
Herpes viruses—except *Herpesvirus simiae* (Monkey B virus) which is in Class 4
Corona viruses
Influenza viruses—all types except A/PR8/34, which is in Class 1
Langat virus
Lymphogranuloma venereum agent
Measles virus
Mumps virus
Parainfluenza virus—all types except *Parainfluenza virus 3, SF4 strain*, which is in Class 1
Polioviruses—all types, wild and attenuated
Poxviruses—all types except *Alastrim, Smallpox, Monkey pox, and Whitepox*, which depending on experiments, are in Class 3 or Class 4
Rabies virus—all strains except *Rabies street virus*, which should be classified in Class 3 when inoculated into carnivores
Reoviruses—all types
Respiratory syncytial virus
Rhinoviruses—all types
Rubella virus
Simian viruses—all types except *Herpesvirus simiae (Monkey B virus) and Marburg virus*, which are in Class 4
Sindbis virus
Tensaw virus
Turlock virus
Vaccinia virus
Varicella virus
Vole rickettsia
Yellow fever virus, 17D vaccine strain

C. *Class 3 Agents*

1. *Bacterial Agents*

Actinobacillus mallei [1]
Bartonella—all species
Brucella—all species
Francisella tularensis
Mycobacterium avium, M. bovis, M. tuberculosis
Pasteurella multocide type B ("buffalo" and other foreign virulent strains [2])
Pseudomonas pseudomallei [1]
Yersenia pestis

2. *Fungal Agents*

Coccidioides immitis
Histoplasma capsulatum
Histoplasma capsulatum var. *duboisii*

3. *Parasitic Agents*

Schistosoma mansoni

4. *Viral, Rickettsial, and Chlamydial Agents*

Alastrim, Smallpox, Monkey pox, and Whitepox, when used *in vitro*
Arboviruses—all strains except those in Class 2 and 4 (Arboriruses indigenous to the United States are in Class 3, except those listed in Class 2. *West Nile* and *Semliki Forest* viruses may be classified up or down, depending on the conditions of use and geographical location of the laboratory.)

[1] USDA permit also required for import or interstate transport.

Dengue virus, when used for transmission or animal inoculation experiments
Lymphocytic choriomeningitis virus (LCM)
Psittacosis-Ornithosis-Trachoma group of agents
Rabies street virus, when used in inoculations of carnivores (See Class 2)
Rickettsia—all species except *Vole rickettsia* when used for transmission or animal inoculation experiments
Vesicular stomatitis virus [2]
Yellow fever virus—wild, when used *in vitro*

D. *Class 4 Agents*

1. *Bacterial Agents*

None

2. *Fungal Agents*

None

3. *Parasitic Agents*

None

4. Viral, Rickettsial, and Chlamydial Agents

Alastrim, Smallpox, Monkey pox, and Whitepox, when used for transmission or animal inoculation experiments
Hemorrhagic fever agents, including *Crimean hemorrhagic fever (Congo)*, *Junin*, and *Machupo* viruses, and others as yet undefined
Herpesvirus simiae (Monkey B virus)
Lassa virus
Marburg virus
Tick-borne encephalitis virus complex, including *Russian spring-summer encephalitis, Kyasanur forest disease, Omsk hemorrhagic fever*, and *Central European encephalitis viruses*
Venezuelan equine encephalitis virus, epidemic strains, when used for transmission or animal inoculation experiments
Yellow fever virus—wild, when used for transmission or animal inoculation experiments

II. Classification of Oncogenic Viruses on the Basis of Potential Hazard (2)

A. *Low-Risk Oncogenic Viruses*

Rous Sarcoma	Rat Leukemia
SV-40	Hamster Leukemia
CELO	Bovine Leukemia
Ad7-SV40	Dog Sarcoma
Polyoma	Mason-Pfizer Monkey Virus
Bovine papilloma	Marek's
Rat mammary tumor	Guinea Pig Herpes
Avian Leukosis	Lucké (Frog)
Murine Leukemia	Adenovirus
Murine Sarcoma	Shope Fibroma
Mouse mammary tumor	Shope Papilloma

B. *Moderate-Risk Oncogenic Viruses*

Ad2-SV40	GaLV
FeLV	HV ateles
HV Saimiri	Yaba
EBV	FeSV
SSV-1	

III. Animal Pathogens (3)

A. *Animal disease organisms which are forbidden entry into the United States by Law (CDC Class 5 agent)*

1. Foot and mouth disease virus

B. *Animal disease organisms and vectors which are forbidden entry into the United States by USDA Policy (CDC Class 5 Agents)*

African horse sickness virus
African swine fever virus
Besnoitia besnoiti
Borna disease virus
Bovine infectious petechial fever
Camel pox virus
Ephemeral fever virus
Fowl plague virus
Goat pox virus
Hog cholera virus
Louping ill virus
Lumpy skin disease virus
Nairobi sheep disease virus
Newcastle disease virus (Asiatic strains)
Mycoplasma mycoides (contagious bovine pleuropneumonia)
Mycoplasma agalactiae (contagious agalactia of sheep)
Rickettsia ruminatium (heart water)
Rift valley fever virus
Rinderpest virus
Sheep pox virus
Swine vesicular disease virus
Teschen disease virus
Trypanosoma vivax (Nagana)
Trypanosoma evansi
Theileria parva (East Coast fever)
Theileria annulata
Theileria lawrencei
Theileria bovis
Theileria hirci
Vesicular exantema virus
Wesselsbron disease virus
Zyonema farciminosum (pseudofarcy)

REFERENCES

1. *Classification of Etiologic Agents on the Basis of Hazard*. (4th Edition, July 1974). U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Office of Biosafety, Atlanta, Georgia 30333.
2. *National Cancer Institute Safety Standards for Research Involving Oncogenic Viruses* (October 1974). U.S. Department of Health, Education, and Welfare Publication No. (NIH) 75-790.
3. U.S. Department of Agriculture, Animal and Plant Health Inspection Service.

Dated: December 15, 1978.

DONALD S. FREDRICKSON,
Director,
National Institutes of Health.

Approved: December 15, 1978.

JULIUS B. RICHMOND,
Assistant Secretary for Health.

Approved: December 15, 1978.

JOSEPH A. CALIFANO, Jr.,
Secretary.

[FR Doc. 78-35533 Filed 12-21-78; 8:45 am]

federal register

FRIDAY, DECEMBER 22, 1978
PART VIII

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

RECOMBINANT DNA

Intent to Propose Regulations

[4110-03-M]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 59]

[Docket No. 78N-0012]

RECOMBINANT DNA

Intent to Propose Regulations

AGENCY: Food and Drug Administration.

ACTION: Notice of Intent to Propose Regulations.

SUMMARY: The Food and Drug Administration (FDA) intends to propose regulations to require assurances in future submissions to the agency that any recombinant deoxyribonucleic acid (DNA) work that has been or will be performed in connection with these submissions fully complies with the National Institutes of Health (NIH) Guidelines for Recombinant DNA Research. This notice is being issued because the Commissioner of Food and Drugs believes it would be helpful to invite public comment on whether such action would be appropriate and desirable.

DATE: Comments by February 20, 1979.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Irvin M. Asher, Office of Health Affairs (HFY-313), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4490.

SUPPLEMENTARY INFORMATION: "Recombinant DNA" molecules have been defined as either (1) molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or (2) DNA molecules that result from the replication of such molecules. (See the FEDERAL REGISTER of July 28, 1978 (43 FR 33042, at 33069).) The Food and Drug Administration has received inquiries from pharmaceutical manufactures and others concerning the use of recombinant DNA techniques in research on, and development and manufacture of, products subject to FDA's jurisdiction.

The Secretary of Health, Education, and Welfare (HEW) has recognized that newly developed techniques for creating and manipulating such molecules constitute scientific tools with unusual promise of bringing about a better understanding and improved treatment of human disease. As scientists in the field were the first to recognize, however, the new techniques pose potential hazards. Should foreign DNA alter microorganisms in unpredictable, undesirable ways, and should those organisms escape from controlled settings, they could conceivably harm individuals and the environment.

On June 23, 1976, NIH issued comprehensive guidelines setting forth appropriate precautions for work with various types of recombinant DNA molecules (see the FEDERAL REGISTER of July 7, 1976 (41 FR 27902)). All Federal agencies that conduct or sponsor research involving recombinant DNA subsequently endorsed the NIH guidelines. At the time the 1976 guidelines were issued, the Director of NIH emphasized that the guidelines were to remain flexible and subject to continuing review as new information relating to potential risks or safety aspects of the research program was developed (see the July 7, 1976 FEDERAL REGISTER at 41 FR 27905).

Since the publication of the 1976 guidelines, the issues surrounding recombinant DNA research have been widely discussed in congressional hearing, public hearings consucted by NIH, and in scientific journals. Proposed revisions of the guidelines were recommended to the NIH Director by the NIH Recombinant DNA Advisory Committee and were published for public comment in the FEDERAL REGISTER, of September 27, 1977 (42 FR 49596). After an extensive evaluation of the September 27 proposal and the comments received in response to that proposal, the NIH Director issued proposed revised guidelines on July 28, 1978 (43 FR 33042). The comments received in response to the July 28 proposal were reviewed by a Departmental review committee established by the Secretary of HEW. That committee's review of the comments, and the new guidelines, are being published in the FEDERAL REGISTER today.

The Commissioner believes that the new NIH guidelines reflect the best available information on recombinant DNA research and constitute the most workable available guide to responsible practice in this developing area of science. They represent the most sophisticated attempt to date to harmonize freedom for scientific inquiry with protection of the public health and environment with respect to this research. The NIH guidelines have been subjected to scientific and public review and will continue to be updated as new information becomes available.

Therefore, the Commissioner intends to propose regulations to require that any firm seeking approval of a product requiring the use of recombinant DNA methods in its development or manufacture demonstrate the firm's compliance with the requirements of the NIH guidelines (in effect at the time work involving recombinant DNA is commenced) in connection with any work it has done or will do relating to that product. Such assurance would be required, for example, in notices of claimed investigational exemption of a new drug (IND's), new drug applications (NDA's), license applications for biologic products, requests for certification for antibiotics, feed additive petitions, food additive petitions, and new animal drug applications (NADA's). Further, the Commissioner intends to propose that the NIH guidelines be incorporated in good manufacturing practice regulations, should recombinant DNA techniques be proposed for the manufacture of products for commercial distribution. Although the details for assuring compliance with the NIH guidelines have not yet been worked out, the Commissioner is considering a requirement that all recombinant DNA research being conducted for submission to FDA be registered with FDA. In evaluating such research, FDA would utilize the expertise of NIH as necessary, and might refer specific protocols to NIH for review as to their compliance with the NIH guidelines.

The Commissioner is aware that product-related research involving recombinant DNA is in many cases regarded as commercially sensitive, and is treated as confidential by persons who conduct or sponsor such research. FDA's public information regulations broadly protect trade secret and commercial information that is privileged or confidential (see 21 CFR 20.61). The regulations (21 CFR 20.82(b)) expressly provide that information within the scope of § 20.61 may not be disclosed.

Moreover, specified types of confidential information are prohibited from disclosure by statute. Section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C 331(j)) prohibits the disclosure, other than to Department employees and to the courts, of any information acquired under authority of specified sections of the act "concerning any method or process which as a trade secret is entitled to protection." The general Federal confidentiality statute, 18 U.S.C. 1905, prohibits the disclosure "in any manner or to any extent not authorized by law" of any information acquired in the course of official duty concerning, among other things, "trade secrets, processes, operation, style of work, or apparatus" of any person (18 U.S.C. 1905).

The regulations to be proposed would provide protections against public disclosure of information con-

cerning the use of recombinant DNA submitted to FDA. In many cases, such information would fall within the protection of section 301(j) of the act as information obtained under FDA's authority regarding research on, or the premarketing approval of, regulated products. Other information would be prohibited from disclosure under 18 U.S.C. 1905. In either circumstance, FDA's regulations proscribe public disclosure of the information, as they do of all information within 5 U.S.C. 552(b)(4). (See 21 CFR 20.61.)

Disclosure of information concerning recombinant DNA to NIH, or to the Recombinant Advisory Committee (RAC), would not affect its status under FDA regulations. The regulations (21 CFR 20.85) provide that information otherwise exempt may be disclosed to "other Federal government departments and agencies" under a suitable agreement restricting further disclosure. Disclosure of this type does not require disclosure to any other person (21 CFR 20.86(b)). Moreover, disclosure to NIH of information within section 301(j) of the act is not inconsistent with that statute, which requires only that information not be released outside HEW.

The Commissioner notes that a technical amendment to § 20.84 of the public information regulations may be required to make clear that exempt information obtained from FDA may be disclosed by NIH to RAC. Any such amendment would restrict such further disclosure to RAC, whose members are retained by NIH as special government employees.

The Commissioner invites public comment on (1) the authority and role of FDA with regard to the use of recombinant DNA techniques to develop and manufacture products that are under its jurisdiction, and (2) whether existing protections for proprietary information are adequate with respect to information that may be submitted to the agency concerning recombinant DNA research.

The Commissioner also invites comments on the following:

1. Are the measures described above the most appropriate? Will they afford the public adequate protection without undue interference in scientific research and product development? What impact would this regulatory approach have on the development of recombinant DNA techniques for commercial production?

2. Are the NIH guidelines suited to an industrial setting or do they need to be revised and, if so, in what respects? For example, is there interest in using a host-vector system other than *E. coli* K-12, which is already approved under the NIH guidelines?

3. Which of the procedural requirements of the NIH Guidelines are inappropriate for an industrial setting? In what way should they be revised?

4. Would any special policies with respect to compliance with, and enforcement of, the contemplated regulations be required?

Comments are invited not only on these questions but on any other questions raised by the contemplated action.

Interested persons may, on or before February 20, 1979, submit to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this notice of intent. Four copies of all comments should be submitted, except that individuals may submit single copies of comments. Comments should be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

Dated: December 13, 1978.

DONALD KENNEDY,
Commissioner of Food and Drugs.

[FR Doc. 78-35534 Filed 12-21-78; 8:45 am]

THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE
WASHINGTON, D.C. 20201

DEC 15 1978

The Honorable Douglas M. Costle
Administrator
Environmental Protection Agency
Washington, D.C. 20460

Dear Doug:

I am announcing today several steps we are taking with respect to the future course of recombinant DNA research in this country. Our objective is to permit the maximum freedom for scientific inquiry consistent with protection of public health and the environment, and with the profound ethical concerns raised by recombinant DNA research.

As noted in the public statement which is enclosed, I am today, (1) approving revised guidelines prepared by the National Institutes of Health governing safety requirements for the conduct of recombinant DNA research by institutions receiving NIH funding for such research; (2) directing NIH to increase its studies on the extent of risk associated with such research; (3) broadening substantially public representation on the HEW advisory committee which will assist NIH in administering the revised guidelines; and (4) increasing significantly public access to information about recombinant DNA research and public participation in administration of the guidelines in local areas.

If the health, environmental and ethical concerns raised by recombinant DNA research are to be accommodated effectively, these actions by government, and by those who receive government support for recombinant DNA research, will not be enough. It is also necessary that research conducted by the private sector comply with the NIH guidelines.

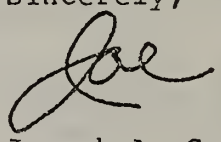
To this end, I have directed the Food and Drug Administration to use its regulatory authority to require that all recombinant DNA research submitted to FDA to satisfy its regulatory requirements comply with the NIH guidelines. I have enclosed FDA's Notice of Intent to Propose Regulations for this purpose.

However, there may be significant recombinant DNA research conducted in the private sector which would not be submitted to the FDA. For this reason, I hope you will review the Environmental Protection Agency regulatory authority and take all action EPA can to require that recombinant DNA research conducted by the private sector complies with the NIH guidelines.

If both FDA and EPA regulate recombinant DNA research, virtually all recombinant DNA research in this nation will comply with the revised NIH guidelines which assure protection of the public health and the environment.

I appreciate your willingness to work with us in this task.

Sincerely,



Joseph A. Califano, Jr.

NATIONAL INSTITUTES OF HEALTH

ADMINISTRATIVE PRACTICES SUPPLEMENT TO THE NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES

December 1978

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service National Institutes of Health

NATIONAL INSTITUTES OF HEALTH

ADMINISTRATIVE PRACTICES SUPPLEMENT TO THE NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES

Policies and Administrative Procedures for
Recombinant DNA Research Subject to the NIH Guidelines

Prepared by the
Office of Recombinant DNA Activities
National Institute of General Medical Sciences
National Institutes of Health
Bethesda, Md., 20014

DECEMBER 1978

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service National Institutes of Health

[60]

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ADMINISTRATIVE PRACTICES SUPPLEMENT

POLICIES AND ADMINISTRATIVE PROCEDURES FOR
RECOMBINANT DNA RESEARCH SUBJECT TO THE NIH GUIDELINES

This Supplement to the NIH Guidelines applies only to recombinant DNA research subject to the Guidelines as revised in December 1978 (See Section I-E of the Guidelines for exempt experiments). The policies and procedures described here may be superseded by subsequent issuances. The NIH Office of Recombinant DNA Activities (ORDA) will publish any changes in the Recombinant DNA Technical Bulletin.

A separate NIH announcement outlines procedures for the transition from the 1976 to the 1978 Guidelines.

I. GENERAL REQUIREMENTS

The requirements in this section of the Administrative Practices Supplement (APS) are mandatory for all recombinant DNA research conducted at Institutions receiving any NIH funds for such research. Additional requirements for NIH applicants and awardees are to be found in Section II.

I-A. Institutional Biosafety Committee (IBC). Each Institution involved in the conduct of recombinant DNA research subject to the Guidelines must have a standing Biosafety Committee. Requirements and recommendations for the composition of such a committee are discussed under Part IV of the Guidelines, which also discusses the roles and responsibilities of Principal Investigators (PIs) and Institutions.

A roster of the members of the Institutional Biosafety Committee (IBC) shall be submitted to ORDA. This must include the names, addresses, occupations, qualifications, and curricula vitae of the chairperson and members of the committee. The information should be addressed to:

Office of Recombinant DNA Activities
National Institutes of Health
Building 31, Room 4A52
Bethesda, Maryland 20014

The membership of IBCs is subject to review by ORDA for compliance with requirements stated in the Guidelines. The Institution shall report promptly to ORDA any changes in this information.

ORDA will assist in the formation of an Area Biosafety Committee (ABC) when appropriate. Such a committee, composed of members from the Institution and other organizations beyond its own staff, may be necessary as an alternative to an IBC when additional expertise from outside a given Institution is necessary for the IBC to fulfill its functions.

I-B. Prior Approval Requirements.

I-B-1. Activities Requiring Prior Approval. An Institution receiving any NIH funds for recombinant DNA research must obtain approval from NIH, or another funding agency designated by NIH for this purpose, prior to the initiation of the following activities:

I-B-1-a. Projects for which containment levels are not explicitly specified by the NIH Guidelines or NIH [The setting of containment

levels for these classes of experiments will require review by NIH, sometimes after recommendation by the Recombinant DNA Advisory Committee (RAC). Hence, investigators are urged to provide to ORDA, in writing, full information on the proposed experiments prior to submission of a formal Memorandum of Understanding and Agreement (MUA)],

I-B-1-b. Projects requiring the P4 level of physical containment,

I-B-1-c. Reductions of more than one step in containment levels for characterized clones (see Section III-A-3 of the Guidelines),

I-B-1-d. Reductions of containment levels for projects involving primate DNA (see Section III-A-3 of the Guidelines),

I-B-1-e. Reductions of containment to levels below P1 + EK1 for purified DNA and characterized clones (see Section III-A-3 of the Guidelines),

I-B-1-f. Initiation of the first project conducted in a facility at the P3 level of physical containment, or

I-B-1-g. Initiation of the first recombinant DNA project subject to the Guidelines at an Institution.

I-B-2. Requests for Activities Requiring Prior Approval.

I-B-2-a. Activities Requiring Prior NIH Approval. MUAs incorporating activities that require prior NIH approval must be submitted to NIH

by the institutional official to whom the IBC is responsible. If the MUA pertains to an NIH-supported project, it must be submitted to the program administrator of the awarding NIH Bureau, Institute, or Division. The latter will forward the request to ORDA. If the MUA pertains to a project supported by private funds or to a project funded by an agency not designated by NIH as having prior-approval authority, the MUA must be submitted directly to ORDA with a covering letter explaining the nature of the request.

I-B-2-b. Activities Approvable by Other Agencies. MUAs pertaining to non-NIH-supported projects and requiring prior approval by the funding agency should be submitted directly to that agency (if it has been designated by NIH as having prior-approval authority).

I-C. Required Registration of Recombinant DNA Projects.

I-C-1. NIH-Supported Projects. For NIH-supported projects, an NIH-approved MUA will constitute registration. (See NOTE ON REGISTRATION in Section II-C below for immediate initiation of projects pending an NIH award.)

I-C-2. Non-NIH Projects Supported by Federal Agencies. Institutions receiving NIH funds for recombinant DNA research which also conduct such research with other Federal funding need not register the latter projects with NIH when the funding agency maintains a registry and provides NIH with certain information.

I-C-3. Nonfederally Supported Projects. Institutions receiving NIH funds for recombinant DNA research must inform NIH of all ongoing nonfederally supported recombinant DNA projects subject to the Guidelines. These projects must be registered with NIH within 30 days of initiation of the project. See Section III of this Supplement for registration procedures for these projects.

I-D. Voluntary Registration. An institution that is not receiving NIH funds for recombinant DNA research may register with NIH any ongoing projects to which the Guidelines are applicable. See Section III of this Supplement for registration procedures for such projects.

II. REQUIREMENTS AND PROCEDURES FOR NIH-SUPPORTED PROJECTS

This section describes additional requirements for NIH-supported projects and applications. The requirements in this section supersede announcements in the October 17, 1977, and February 15, 1978, issues of the NIH Guide for Grants and Contracts and notices in application kits for Public Health Service research and training grants.

II-A. Memorandum of Understanding and Agreement (MUA). Each research grant application to the National Institutes of Health for a project involving experiments subject to the NIH Guidelines for Recombinant DNA Research (see Section I-E of the Guidelines for exempted experiments) must be accompanied by an MUA. Applicants are urged to follow as closely as possible the sequence and format of the Illustration

below. See Section II-A-3 for procedures for other classes of NIH awards.

II-A-1. Elements of an MUA. An MUA must contain the following sections:

II-A-1-a. Description. There must be a description of each proposed project, and the name of the individual investigator responsible for the research if other than the Principal Investigator.

Descriptions must include information on (i) the source(s) of DNA, (ii) the nature of inserted DNA sequences, and (iii) the hosts and vectors to be used. The descriptions must provide sufficient information about the experiments so that reference to other documents is not required. For each performance site, the organization name(s), the city, and the State must be stated. The description for each series of experiments can ordinarily be held to two pages.

II-A-1-b. Assessment of Containment Levels. There must be an assessment of the physical and biological containment levels required by the NIH Guidelines for each series of experiments, with citation of the relevant sections of the Guidelines or announcements from ORDA.

II-A-1-c. Information on Health Surveillance. Information must be provided on the Institution's determination of the necessity, in connection with each project, for health surveillance of recombinant DNA

research personnel. Information must also be provided on the nature of the health surveillance program, if instituted.

II-A-1-d. Statement on Shipping and Accuracy of MUA. The principal investigator must provide a specific brief statement (i) agreeing to abide by the provisions of the NIH Guidelines and the requirements of this Supplement concerning shipment and transfer of recombinant DNA materials, and (ii) attesting to the accuracy of the information in the MUA (see item d in Illustration).

II-A-1-e. Information Concerning IBC Review. A certification is required that the IBC has reviewed the proposed project and found it to be in compliance with the NIH Guidelines, this Supplement, and other specific NIH instructions. The date of review by the IBC must be specified.

When facilities are proposed, under construction, or in renovation at the time the MUA is reviewed, the IBC review must include an assurance that recombinant DNA experimentation will not occur until the IBC has surveyed the completed facility, found it to be in compliance with the Guidelines, and verified that an amended MUA has been submitted to NIH.

NOTE: Some MUAs may have to incorporate a certification as well as an assurance if both certified facilities and facilities under construction or renovation are involved.

II-A-1-f. Statement Regarding Training and Continuing Compliance. The appropriate institutional official must submit a statement that the institution agrees to accept responsibility for the training of all laboratory workers involved in the project, and that the IBC will ensure compliance with the Guidelines throughout the duration of the project.

II-A-1-g. Signatures. The signatures of the Principal Investigator, the IBC chairperson, and the institutional official(s) are required. The Institution may designate the IBC chairperson as the responsible institutional official, except for projects requiring prior approval by NIH (see Section I-B).

II-A-1-h. Date of MUA. For future reference, the date of the MUA will be the date of the institutional official's signature.

II-A-2. MUAs for Recombinant DNA Research at Multiple Sites. When research at multiple sites is proposed, the MUA must specify where each portion of the project will be carried out. When research is proposed at sites governed by other than the applicant Institution, signatures of the appropriate officials at both the applicant Institution and the Institution(s) where the recombinant DNA research is to be conducted are required. The signatures shall indicate that the IBCs of each of the Institution(s) where the research is to be performed have given the certification and/or assurance required in Section II-A-1-e of the MUA.

II-A-3. MUAs Associated with Individual Fellowship Applications, Research Career Development Award Candidates (RCDA), Research Career Awardees (RCA), and National Research Service Awards. When projects involving recombinant DNA technology subject to the Guidelines are involved, fellowship applicants, RCDA candidates, RCAs, or program directors for National Research Service Fellowship applications must either file a copy of an MUA(s) already submitted to the NIH or submit a new MUA(s) as indicated below. MUAs for these classes of applications need not be filed at the time the application is submitted, but must be filed with the program administrator of the awarding NIH Bureau, Institute, or Division when an award is made and before recombinant DNA research is initiated. These procedures also apply to experiments using recombinant DNA technology in courses supported by an institutional fellowship.

If a copy of an existing MUA is submitted, the fellowship applicant, RCDA candidate, RCA, or program director (if other than the Principal Investigator) must sign the MUA under the signature of the PI.

If any recombinant DNA work is proposed other than that described in an existing MUA, a new or amended MUA must be submitted to NIH.

II-B. Notation on Applications for Research and Training Grants. NIH application forms will be revised to include a block indicating whether recombinant DNA research subject to the Guidelines is involved.

Until such revised forms are available, the following statement must appear at the bottom of the first page of the application:

APPLICATION INVOLVES EXPERIMENTS SUBJECT TO GUIDELINES FOR RECOMBINANT DNA RESEARCH

II-C. Submission of Memorandum of Understanding and Agreement (MUA).

II-C-1. Competing Applications. Applications for competing research grants involving recombinant DNA research subject to the Guidelines must include an MUA when submitted to the Division of Research Grants, NIH. An application submitted without an attached MUA is incomplete and will not be reviewed until a properly executed MUA is provided. (See Section II-A-3 for procedures for other types of applications.)

II-C-2. Noncompeting Applications. Applications for noncompeting continuation grants involving recombinant DNA research subject to the Guidelines must be accompanied by an updated MUA indicating that the IBC has reviewed the project and found it to be still in compliance with the NIH Guidelines.

NOTE ON REGISTRATION: If an investigator submitting a new competing application to NIH and prior to its funding wishes to initiate a project upon IBC approval, the procedures for registration of non-NIH projects, described in Sections I-C-2, I-C-3, or III-A of this Supplement, must also be followed. Initiation of new experiments in an ongoing project requires that an MUA be filed with NIH within 30 days of IBC approval, even if the proposed experiments are also described in an MUA submitted with a noncompeting or a competing renewal application that may be funded at a later date. In these cases, the procedures dealing with changes in ongoing projects, described in Section II-E of this Supplement, must also be followed.

II-D. Review of MUAs by NIH. ORDA will review all MUAs for projects funded, or about to be funded, by NIH. The Principal Investigator and the IBC will be notified of the NIH review of the MUA. If ORDA finds that an MUA, or certain aspects of it, do not conform to standards set forth in the Guidelines, immediate action must be taken to bring the protocols into compliance or the experiments in question must be suspended.

II-E. Changes in Ongoing Projects. Changes in a project subject to the Guidelines must be reported to the IBC by the Principal Investigator.

II-E-1. Protocols for Which Prior NIH Approval Is Not Required. The procedures described in this section apply only to protocols for which prior NIH approval is not required (see Section I-B of this Supplement for prior approval requirements). Depending upon the IBC's judgment as to whether the proposed changes are major or minor, the procedures described in Sections II-E-1-a and -b below are to be followed.

II-E-1-a. Major Changes. A new or revised MUA is required for major changes in the recombinant DNA aspects of an ongoing project. Examples of such changes are (i) a significant change in hosts or vectors, (ii) a significant change in the donor species or the nature of the DNA segment selected, (iii) a major change in the physical location of the experiments, or (iv) a change of the responsible investigator.

For such major changes, a new or revised MUA must be submitted to the IBC. Once the IBC has approved a project not requiring prior NIH approval (see Section I-B of this Supplement), the experiment(s) may be initiated. The Institution must then forward the MUA directly to the program administrator of the awarding NIH Bureau, Institute, or Division within 30 days of the IBC approval. The MUA must identify the project by grant number. The Principal Investigator and the IBC will be notified regarding the NIH review of the new or revised MUA. If ORDA finds that an MUA, or certain aspects of an MUA, do not conform to standards set forth in the Guidelines, immediate action must be taken to bring the

protocols into compliance or the experiments in question must be suspended.

II-E-1-b. Minor Changes. Principal Investigators should submit information on minor changes in research protocols to the IBC. Minor changes need not be reported to NIH until an updated MUA is required (see Section II-C-2 of this Supplement).

II-E-2. Protocols for Which Prior NIH Approval Is Required. Prior NIH approval is required for changes involving recombinant DNA experiments described in Section I-B of this Supplement.

II-F. Shipping Requirements. Certification of compliance with requirements for shipment and transfer of recombinant DNA materials may be incorporated in the MUA (as shown in item d of the Illustration below). All MUAs must indicate that the Principal Investigator (program director, fellow, or candidate) agrees to comply with the following provisions:

II-F-1. Prior to shipment or transfer of recombinant DNA materials within the United States, the sending laboratory shall obtain a written statement from the requesting laboratory that:

II-F-1-a. Research involving recombinant DNA molecules shall be conducted in compliance with the NIH Guidelines and other NIH instructions, and

II-F-1-b. The project proposed by the requesting laboratory has been reviewed and approved by the IBC overseeing that laboratory.

II-F-2. Prior to shipment of recombinant DNA materials to a foreign country, the sending laboratory shall obtain from the requesting laboratory a statement that the research involving recombinant DNA molecules will be conducted in accordance with the containment standards of the NIH Guidelines, or under applicable national guidelines.

II-F-3. The sending investigator shall maintain a record of all shipments of recombinant DNA materials.

NOTE: See Section II-D-3 of the Guidelines for restrictions on distribution of certified host-vector systems.

II-G. Policy and Procedures for Recombinant DNA Research Supported by NIH and Conducted in Foreign Countries.

II-G-1. Requirements Regarding Countries That Have Adopted Guidelines. Many countries in which NIH-supported recombinant DNA research may be conducted have adopted guidelines for this research which are either comparable to or based on principles similar to those of the NIH Guidelines. Also, many countries have organizations and procedures to review and register recombinant DNA research, and require documentation similar to that of NIH. If such comparable guidelines and procedures exist, then review and approval by the appropriate national body of the country in which the research is to be conducted will, in

general, be accepted as assurance that the research will be conducted in a responsible manner. NIH reserves the right, however, to withhold funding if the safety practices to be employed are not reasonably consistent with the NIH Guidelines.

The following procedures apply to NIH-supported research in foreign countries that have adopted guidelines, whether the investigators are U.S. or foreign nationals. For U.S. investigators intending to conduct recombinant DNA research abroad, the required documentation (see below) must be submitted prior to initiation of the project. For applications by foreign nationals, the required documentation may be included with the application or submitted at a later date, but it must be submitted prior to the time of award.

In the above cases, a document providing the following information must be submitted to NIH:

II-G-1-a. A description of each proposed project, and the name of the individual investigator responsible for the research if other than the Principal Investigator. The description must include information on the sources of DNA, the nature of inserted DNA sequences, and the hosts and vectors to be used. It must provide enough detail to obviate the need for reference to other documentation. Ordinarily, each series of experiments should require no more than two pages of description.

II-G-1-b. An assessment of the level(s) of physical and biological containment required by the guidelines of the country in which the research is to be conducted.

II-G-1-c. Documentation that the research project is in compliance with the applicable national guidelines and, where required, has been registered with the appropriate national body. If approval of the national body is required prior to initiation of the research, the documentation must indicate that such approval has been received.

II-G-1-d. The signatures of both a responsible official and the Principal Investigator.

II-G-1-e. The date of signature of the responsible official. This will become the date of the document for future reference.

II-G-2. Requirements Regarding Countries That Have Not Adopted Guidelines. NIH funds may not be used for the conduct of recombinant DNA research in a country that has not adopted national guidelines unless the research is in full compliance with the NIH Guidelines and with the procedures required for U.S. grant applications -- i.e., an IBC must be established, an MUA filed, etc.

II-H. Lowering of Containment Levels for Purified DNA and Characterized Clones.

II-H-1. Purified DNA Other Than Plasmids, Bacteriophages, and Other Viruses. The Guidelines stipulate that the formation of DNA recombinants from cellular DNAs that have been purified and for which the absence of harmful sequences has been established can be carried out under lower containment conditions than those required for the corresponding shotgun experiment. IBC approval is sufficient for such a reduction of containment level, except for (i) primate DNA, which also requires prior NIH approval, or (ii) any lowering of containment to levels below P1 + EK1, which also requires prior NIH approval (see Section III-A-3-a of the Guidelines).

The IBC must notify ORDA in writing of all such actions. Many of these notifications will be in the form of a new or revised MUA.

II-H-2. Characterized Clones of DNA Recombinants. The Guidelines permit IBCs to give approval for a single-step reduction in physical or biological containment on receipt of evidence of (i) characterization of a clone derived from a shotgun experiment and (ii) the absence of harmful sequences (see Section III-A-3-b of the Guidelines). IBC approval is sufficient for such a reduction except for (i) primate DNA which requires prior NIH approval, (ii) any lowering of containment to levels below P1 + EK1, which also requires prior NIH approval or (iii) any lowering of containment by more than one step in either physical or biological containment [see Section III-A-3-b-(2) of the Guidelines)]. The IBC must

notify ORDA in writing of all such actions. Notification must clearly indicate the name of the Principal Investigator and identify the project.

Prior NIH approval is required for the use of primate DNA, reduction of containment by more than one level, or reduction to levels below P1 + EK1. In these three cases, complete information must be submitted to ORDA.

II-I. Exceptions to Prohibitions and Exemptions from the Guidelines.

II-I-1. Exceptions. Requests for exceptions to prohibited experiments (see Guidelines, Section I-D) must be submitted with the concurrence of the IBC. Such exceptions require express approval by the Director, NIH, with advice of the Recombinant DNA Advisory Committee (RAC) after appropriate notice and opportunity for public comment [see Section IV-E-1-b-(1) of the Guidelines].

II-I-2. Exemptions. Classes of experiments that are exempt from the Guidelines are cited in the Guidelines, Section I-E. It is anticipated that additions to the lists under I-E-4 and I-E-5 will be approved by the Director, NIH, on the RAC's recommendation and after appropriate notice and opportunity for public comment.

II-I-3. Requests for Exceptions and Exemptions. Requests for an exception to a prohibition or an exemption from the Guidelines must be submitted to ORDA, with adequate documentation. Because the handling of

requests for exceptions and exemptions will involve review by the RAC and provisions for public comment, investigators are urged to discuss the proposal with ORDA before submitting a formal request. Decisions on requests for exceptions or exemptions will be published in the Federal Register and the Recombinant DNA Technical Bulletin.

III. PROCEDURES FOR REGISTRATION OF NONFEDERALLY SUPPORTED PROJECTS AND FOR VOLUNTARY REGISTRATION

III-A. Mandatory Registration. Institutions receiving NIH funds for recombinant DNA research must inform NIH of all such research, ongoing and nonfederally supported, to which the Guidelines are applicable.

III-B. Voluntary Registration. The Guidelines stipulate that any institution that is not receiving NIH funds for recombinant DNA research may nevertheless register with the NIH any ongoing projects to which the Guidelines are applicable. At the present time, however, proprietary information should not be submitted to this register.

III-C. Procedures for Registration. The procedures in this section apply to registration of projects under III-A and III-B above. Because nonfederally supported projects filed with NIH will immediately be added to the register of ongoing recombinant DNA research, institutions may register only those projects that are ongoing or about to be

initiated. Institutions must not submit pending projects to this register.

Institutions must register directly with ORDA projects described in Sections III-A and III-B. It is the responsibility of the Institution to ensure that this information is accurate and up-to-date by submitting any necessary revised information on a timely basis. Institutions should notify ORDA when a project is completed or terminated so that it may be removed from the register.

III-C-1. For registration of projects described in Sections III-A and III-B above, the following information must be submitted:

III-C-1-a. A short title for the project.

III-C-1-b. Registry number of the project. This is to be a unique number, not to exceed five digits, assigned by the Institution.

III-C-1-c. Starting and ending dates of the project.

III-C-1-d. The name of the Principal Investigator and the name and address of the Institution. The department in which the research is conducted and the location of the project should be included.

III-C-1-e. The source of support for the project.

III-C-1-f. A description of each project and the name of the responsible investigator. Descriptions should include information on

(i) the source(s) of DNA, (ii) the nature of inserted DNA sequences, and (iii) the host-vector system(s) being used. Ordinarily, no more than two pages of description for each series of experiments are necessary.

III-C-1-g. An assessment of the level(s) of physical and biological containment required by the Guidelines for each series of experiments.

III-C-1-h. A statement that an Institutional Biosafety Committee (IBC) has reviewed the project and found it to be in compliance with the NIH Guidelines.

III-C-1-i. The signatures of the Principal Investigator, the chairperson of the IBC, and the institutional official. The Institution may designate the IBC chairperson as the responsible institutional official.

III-C-1-j. The date of signature by the institutional official. This date will be used for reference purposes.

III-D. Review of Non-NIH-Supported Projects. Institutions and Federal agencies will be notified in writing of ORDA's review of the information submitted for registration of recombinant DNA projects not supported by NIH. If review by ORDA finds that the protocols do not conform to standards set forth in the Guidelines, the Institution shall take appropriate action to bring the protocols into compliance.

Illustration

NAME OF INSTITUTION

MEMORANDUM OF UNDERSTANDING AND AGREEMENT

Application/Grant Number (if applicable) _____

Investigator's Telephone Number _____

a. Description

(To be supplied)

b. Assessment of Levels of Physical and Biological Containment

(To be supplied)

c. Information on Health Surveillance

(To be supplied)

d. I agree to comply with the NIH requirements pertaining to shipment and transfer of recombinant DNA materials. I am familiar with and agree to abide by the provisions of the current NIH Guidelines and other specific NIH instructions pertaining to the proposed project. The information above is accurate and complete.

_____

Principal Investigator Date

e. I certify that the Institutional Biosafety Committee (IBC) has reviewed on (date) the proposed project for recombinant DNA experiments and has found it to be in compliance with the NIH Guidelines and other specific NIH instructions pertaining to the proposed project.

AND/OR

I assure that the IBC has reviewed on (date) the proposed project and the plans for facilities proposed or under construction or renovation. Recombinant DNA experimentation will not occur until the completed facilities have been reviewed by the IBC and an MUA with certification has been submitted to NIH.

f. The Institution agrees to accept responsibility for the training of all laboratory workers involved in the project. The IBC will monitor throughout the duration of the project the facilities, procedures, and the training and expertise of the personnel involved in the recombinant DNA activity.

g. _____
IBC Chairperson Date

h. _____
Applicable Institutional Official Date

_____
Institutional Official Date
(additional performance sites, if applicable)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

December 15, 1978

M E M O R A N D U M

TO: Institutional Biosafety Committees and Principal Investigators

FROM: Director
Office of Recombinant DNA Activities, NIH

SUBJECT: Transition to Revised Guidelines for Recombinant DNA Research

I. Revised Guidelines for Recombinant DNA Research

The revised NIH Guidelines for Research Involving Recombinant DNA Molecules will be published in the Federal Register within the next two weeks. An Administrative Practices Supplement, formerly Appendix C, will be published separately to provide information on administrative procedures to be followed under the revised Guidelines.

The purpose of the present document is to provide guidance on appropriate prpcedures for transition to the revised Guidelines.

II. Effective Date of Revised Guidelines

The revised Guidelines are effective January 2, 1979, and may be implemented on that date provided that the requirements set forth below have been fulfilled.

III. Institutional Biosafety Committees

Institutional Biosafety Committees (IBCs) must be in compliance with new requirements before they can proceed to evaluate MUAs under the revised Guidelines. Section IV-D-2 of the revised Guidelines should be consulted for complete information on the membership and procedures of an Institutional Biosafety Committee (IBC).

Among the revised requirements is that the IBC shall be composed of no fewer than five members so selected that they collectively have experience and expertise in recombinant DNA technology and the capability to assess the safety of recombinant DNA research experiments and any potential risk to public health or the environment. At least two members (but not less than 20 percent of the membership of the committee) shall not be affiliated with the Institution (apart from their membership on the IBC) and shall represent the interest of the surrounding community with respect to health and protection of the environment. Members meet the latter requirement if, for example, they are officials of State or local public health or environmental protection agencies, members of other local governmental bodies, or persons active in medical, occupational health, or environmental concerns in the community. The Biological Safety Officer (BSO), mandatory when research is being conducted at the P3 and P4 levels, shall be a member (see Section IV-D-4). See Section IV-D-2 for additional requirements and recommendations for the operations of IBCs.

All institutions receiving NIH funds for recombinant DNA research must file a report with ORDA no later than January 31, 1979, indicating that the IBC is in compliance with the requirements of the revised Guidelines. Even if an IBC already on file with ORDA meets the requirements of the revised Guidelines, a statement to that effect must be filed. If new members have been appointed to effect this compliance, a revised list of members and additional CVs should accompany the report. IBCs will be notified of the review of their composition for compliance with the requirements of the revised Guidelines.

Institutions may begin to use the revised Guidelines in accordance with procedures in Sections IV and V as soon after January 2, 1979, as they have an IBC so constituted that it meets the revised requirements. Prior NIH approval of the IBC membership is not required.

IV. Ongoing Projects and Adoption of New Containment Levels

Ongoing projects being carried out under the provisions of the 1976 Guidelines and covered by approved MUAs on file with NIH should continue under the same containment levels until newly executed MUAs, specifying containment requirements of the revised Guidelines, have been approved by a properly constituted IBC. Institutions must then submit the new MUA within 30 days of IBC approval to the appropriate program administrator of the awarding NIH Bureau, Institute, or Division. The revised MUA must include a reference

to the original MUA in order to facilitate appropriate changes in the ORDA registry of ongoing research.

When IBC approval has been obtained for projects other than those requiring prior NIH approval (see below), the experiments may be initiated.

V. Prior Approval Requirements

Under the revised Guidelines, an institution receiving NIH funds for recombinant DNA research must obtain approval from NIH, or another funding agency designated by NIH for this purpose, prior to initiation of the following activities (See Section I-B of the Administrative Practices Supplement):

- Projects for which containment levels are not explicitly specified by the NIH Guidelines or NIH. (The setting of containment levels for these classes of experiments will require review by NIH, often after recommendation by the Recombinant DNA Advisory Committee. Investigators are urged to provide to ORDA, in writing, full information on the proposed experiments prior to submission of a formal MUA),

- Projects requiring the P4 level of physical containment,

- Reductions of more than one step in containment levels for characterized clones (see Section III-A-3 of the Guidelines),

- Reductions of containment levels for projects involving primate DNA (see Section III-A-3 of the Guidelines),

- Reductions of containment to levels below P1 + EK1 for purified DNA and characterized clones (see Section III-A-3 of the Guidelines),

- Initiation of the first project conducted in a facility at the P3 level of physical containment,

- Initiation of the first recombinant DNA project subject to the Guidelines conducted at an institution. (Institutions which have already had an NIH-approved MUA satisfy this requirement).

MUAs incorporating activities that require prior NIH approval must be submitted to NIH by the institutional official to whom the IBC is responsible. If the MUA pertains to an NIH-supported project, it must be submitted to the program administrator of the awarding NIH Bureau, Institute, or Division. The latter will forward the request to ORDA. If the MUA pertains to a project supported by private funds or to a project funded by an agency not designated by NIH as having prior approval authority, the MUA must be submitted directly to ORDA with a covering letter explaining the nature of the request.

VI. Exempt Projects

IBCs should inform ORDA and the appropriate NIH program administrator of ongoing projects that are exempt from the requirements of the revised Guidelines, so that these projects may be removed from the NIH registry of recombinant DNA projects covered by Guidelines (see Section I-E of the Guidelines for exempt experiments).

VII. Containment Conditions Specified by NIH

In a number of cases NIH has stipulated appropriate containment levels for experiments that were not specifically considered under the 1976 Guidelines and are also not specifically considered in the revised Guidelines. The containment levels for these experiments were specified by NIH after recommendation by the RAC and approval by the Director, NIH. These experiments may continue, without new MUAs, under the stipulated containment conditions. Requests for changes in the stipulated containment conditions must be processed according to procedures described in the Administrative Practices Supplement.

William J. Gartland, Jr., Ph.D.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

PUBLIC HEARING ON THE PROPOSED

REVISED GUIDELINES ON RECOMBINANT DNA RESEARCH

Conference Room 529-A
Hubert H. Humphrey Building
200 Independence Avenue, S.W.
Washington, D. C.

Friday, September 15, 1978

Met, pursuant to notice, at 9:20 a.m.

BEFORE:

MR. PETER LIBASSI, Chairman
General Counsel
Department of Health, Education, and Welfare

DR. DONALD FREDRICKSON
Director
National Institutes of Health

DR. JULIUS RICHMOND
Assistant Secretary for Health
Department of Health, Education, and Welfare

DR. HENRY AARON
Assistant Secretary for Planning & Evaluation
Department of Health, Education, and Welfare

APPEARANCES:

ROBERT M. BOCK
Federation of American Societies for
Experimental Biology

LESLIE DACH
Environmental Defense Fund

JUNE E. OSBORN
Professor, University of Wisconsin

APPEARANCES: (Continued)

HARLYN O. HALVORSON
American Society for Microbiology

CONGRESSMAN RICHARD L. OTTINGER
U. S. House of Representatives

W. J. WHELAN
Committee on Genetic Experimentation,
Internatinal Council of Scientific Unions

ROBERT M. FAUST
U.S. Department of Agriculture

DHUN B. PATEL
New Jersey Department of Health

PHILIP L. BEREANO
Associate Professor, University of Washington

DEBORAH W. FEINBERG
New York Attorney General's Office

NORTON ZINDER
Professor, Rockefeller University

PAMELA T. LIPPE
Friends of the Earth

JONATHAN KING
Associate Professor, Massachusetts
Institute of Technology

THOMAS BLESSING
Wastenaw County, Michigan, Drain Commissioner

L. CHRISTINE OLIVER
Oil, Chemical, Atomic Workers International Union

CARL E. KLINE
Western Maryland Clergy and Laity Concerned

DANIEL F. LIBERMAN
Biohazard Assessment Officer, Massachusetts
Institute of Technology

GRACE UNGERS
Sloan-Kettering Institute

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CARL W. ANDERSON
Brookhaven National Laboratory

NANCY PFUND
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CHARLES P. EMERSON
Associate Professor, University of Virginia

RICHARD HARTZMAN
Friends of the Earth

DAVID COPLIN
Assistant Professor, Ohio State University
Agricultural Center

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P R O C E E D I N G S

(9:20 a.m.)

MR. LIBASSI: My name is Peter Libassi. I am the General Counsel of HEW and the Chairman of the Task Force. On my immediate right is Dr. Fredrickson, Director of the National Institutes of Health, who is Vice Chairman of the Task Force with me. On my left is Dr. Julius Richmond, the Assistant Secretary for Health and the Surgeon General. And on my far right is Dr. Henry Aaron, the Assistant Secretary for Planning and Evaluation.

The purpose of this hearing this morning is to receive public comments on the National Institutes of Health's proposed revisions in the guidelines for the conducting of recombinant DNA research.

Secretary Califano has asked that we hold this hearing in connection with NIH's solicitation of public comments on these revisions, which were published in the Federal Register on July 28, 1978. These proposed revisions reflect NIH's experience with the current guidelines since they were published in 1976, and NIH has subjected the existing guidelines to extensive discussion and debate, both within the scientific community and in the broader general public.

The hearing is, nevertheless, appropriate because of the importance of this subject and the

public interest it has attracted. In calling for this hearing, Secretary Califano specifically asked that we seek comments on several issues, particularly the sections of the proposed revised guidelines that establish the mechanism for administering and revising the guidelines, including the procedures that would allow for otherwise prohibited experiments and the procedures for exempting certain classes of research from the guidelines completely.

In addition, he asks that we look at the standards for the exercise of administrative discretion under the guidelines by the Director of NIH, and for the composition of the various public and scientific and advisory bodies that are mentioned in the guidelines, particularly the Recombinant DNA Advisory Committee, and the institutional biosafety committees at the local level.

So that is the general area of our interest. However, we will be glad to hear comments from anyone on any aspect of the revised guidelines. We are looking at all issues and all aspects as we proceed with this final review.

Now, because of the number of witnesses who have asked to appear, we are asking that they limit themselves to ten minutes each. Some have submitted

statements already, and your statements will be made a part of the record in full, so that it isn't necessary for you to read the entire statement. We would like you to present a summary of your statement, and, if possible, not to use all of your ten minutes, so that we may have an opportunity to ask questions within the ten minutes allotted to each speaker. But if you feel you would like to speak for the full ten minutes and not hear us ask questions, you can do that also.

We will go through a list of speakers, but we have tremendous staying power on the Task Force, and we will stay until everybody who wishes to make a comment or make a statement is heard, even though you have not signed up in advance. If people will simply let the staff know that they would like to make a statement, we will put you at the end of the list, and we will stay as long as we possibly can to hear everybody.

Now, with that, I believe, we can go to the list. The first speaker is Robert M. Bock. If you would come forward and identify yourself for us, then you can begin.

Leslie Dach is the second witness. If you wouldn't mind just taking a seat behind, and June Osborn is the third witness, and there is a third chair, and that way we will move it along as quickly as possible.

At the end of nine minutes there is a kitchen clock that will ring, and at the end of ten minutes, the trap door opens, and you disappear.

(Laughter.)

Go ahead now.

DR. BOCK: Mr. Chairman, ladies and gentlemen, I am Robert Bock. I am the Dean of the Graduate School of the University of Wisconsin at Madison, and I am the Vice Chairman of the Public Affairs Committee of the Federated American Societies of Experimental Biology.

Although scientists have been aided by the powerful new tool of recombinant DNA technology for only a few years, dramatic advances in the understanding of genetics, the structure and organization of chromosomes, and the detailed regulatory processes controlling replication and metabolism have already been published. This new knowledge has provided a more sound basis for modern concepts of many processes of metabolism in normal and diseased organisms. Practical applications for health care, agriculture, and environmental protection have appeared more slowly, yet significant progress has been reported in producing materials of potential value to society.

The proposed Revised Guidelines for Recombinant DNA Research are reasonable, cautious, and careful

advances toward policies and practices which will provide society with protection from biological hazards while permitting society to benefit from the major advances in knowledge made possible by these techniques. The proposed revisions are a marked advance from the 1976 edition, because expert input on infectious diseases and pathogenicity has been the basis for the revision of classifications and procedures.

It must be recognized that the proposed revisions are a needed step in an evolving process. As scientific data continues to be gathered, improved technical approaches should be considered and introduced. Any problems encountered should impact our practices, and the goal of safe, efficient practices, clearly defined and well understood by all, should remain before us.

The revised guidelines are to be commended for their use of good data on the known normal defense mechanisms of living organisms and the protection of individuals who are at special risk because of impairments in these normal defense mechanisms.

While the revised guidelines recognize that the biological safety committees are involved in numerous important tasks other than recombinant DNA technology, there should be considerable caution in further demands on these committees, which could distort their efforts

out of proportion to the need to instruct, advise, and assure proper practice with known biological hazards of all kinds. These committees have broad responsibilities that go far beyond recombinant DNA technology.

The guidelines may be overly presumptive in mandating a specific style of lay representation for this particular committee, when many universities have already installed lay overview at several levels, including their boards of regents, boards of public visitors, university/community liaison committees, et cetera. In contrast to the human subjects committees, where broad concepts of social and ethical values are necessary to the very function of the committee, the biological safety committee is an expert committee which needs breadth in expertise and which should not be diverted from its primary responsibility of safety.

I would call your particular attention to Section IV, where the roles and responsibilities of the various participants in this process are considered. These roles and responsibilities should be taken as a section which needs evaluation in practice. It should be discussed as a priority matter in any subsequent revision, and consideration be taken of new legislation and operational experience. Clearly, when an expert panel such as the Recombinant DNA Advisory Committee proposes that there

needs to be an exception to the guidelines, the Director should be authorized to disapprove or to approve that proposal.

Thank you.

MR. LIBASSI: Are there any questions from any members of the panel?

Thank you, no.

The next witness is Mr. Leslie Dach.

MR. DACH: Good morning. My name is Leslie Dach. I am a Science Associate with the Environmental Defense Fund. EDF is a nonprofit organization with over 46,000 members that undertakes judicial, legislative, and administrative actions to minimize human exposure to toxic chemicals. EDF has been deeply involved in the national debate on recombinant DNA. In '76 we petitioned the Department of HEW to use its authority under Section 361 of the Public Health Services Act to regulate recombinant DNA activities.

Since that time EDF has submitted comments on the current NIH recombinant DNA guidelines, and has testified before Congress and the Advisory Committee to the Director of NIH on this issue.

EDF thanks the Secretary for holding this public meeting. Because of the limited time allotted to each speaker, I will only be able to touch on a small number of

our concerns, but we intend to submit extensive written comments on the proposed guidelines.

I would briefly like to discuss the following five aspects today: One, the need to rewrite sections of the guidelines to eliminate ambiguity; two, mechanisms for assuring adequate public participation in NIH activities mandated by the guidelines; three, membership in the Recombinant DNA Advisory Committee; four, membership and responsibilities of the institutional biohazard committees; and five, confidentiality.

EDF is concerned that the poor quality of the drafting of the guidelines will result in confusion and compliance failures. There are many sections of the guidelines that you can pore over for hours and still not fully understand what is required.

As presently written, instructions for persons conducting DNA activities are spread throughout the guidelines themselves, the Director's decision document, the Environmental Impact Assessment, and appendices to these documents. And often these documents contradict each other. But only the guidelines have the indisputable force of law.

Moreover, the guidelines are sometimes so vague that their intent is unclear, and problems are sure to arise.

The section of the guidelines dealing with certification of host-vector systems is an example of the problematic ambiguity. The guidelines state that certain new host-vector systems, "may not be used unless they have been certified by NIH." But there is no indication of what office within NIH would supply the certification. The person seeking certification does not know if he or she is free to use the host-vector system after approval by the Recombinant DNA Advisory Committee, or if they must wait for approval of the NIH Director. Just this ambiguity was cited by the University of California at San Francisco to explain their violation of the existing guidelines, yet it has not been cleared up in the present draft.

An example of the contradictory nature of the various documents in the Federal Register package is a section dealing with exceptions from prohibited experiments. The Director's decision document indicates that the rationale for allowing exceptions is to provide for experiments for which there are compelling social or scientific reasons. Yet the guidelines themselves merely indicate that weight will be given in the decision-making process to "both scientific and social benefits and to potential risks." Clearly, the standard for excepting experiments is different in

the two documents.

When differing interpretations of the same issue are given in different sections of the Federal Register package, it is impossible for EDF, any other commentator or a person conducting recombinant DNA activity to ascertain what the correct interpretation is. In addition, it is unrealistic to assume that every reader will scour all the documents in the Federal Register. Most importantly, the Environmental Impact Assessment and the Director's decision document again do not have the indisputable force of law.

EDF therefore maintains that all information necessary for compliance must be included in the guidelines themselves, and that ambiguities within the guidelines must be clarified.

The second area of concern I will discuss today is the failure of the guidelines to specify procedures for public notification and comment. The guidelines often indicate that a decision will be made "after appropriate notice and opportunity for public comment." However, no further clarification of this notion is ever given. The procedures for public notification and comment must be described in detail in the guidelines. Failing this, the public will have no assurance that opportunity for public comment indeed will be provided if pressure for a quick

decision is strong or NIH wishes to avoid public scrutiny. The guidelines enable the agency to make decisions in secret.

As an example of how public participation mechanisms should be constructed, EDF proposes the following for decisions concerning exceptions from prohibited experiments. Within ten days of receipt of an application for exception from a class of prohibited experiments, NIH should publish in the Federal Register notice of the receipt, details of where the material submitted in support of the application can be obtained by the public, and the closing date of the public comment period. At minimum, the comment period should be 45 calendar days. Final notice of agency action should also be published in the Federal Register, and all materials submitted to NIH should be available to the public.

The third area of our concern is the membership of the Recombinant DNA Advisory Committee, RAC. RAC decisions involve weighing both social and scientific risks and benefits. This is especially true for allowing exceptions from classes of prohibited experiments. Such decisions are clearly not purely scientific ones. As such, RAC must include nonscientist members who adequately represent the interests of the general public. The guidelines do not provide for this.

EDF suggests that at least one-third of RAC be composed of individuals who are not enaged in biomedical research, and who can reasonably be expected to represent the interests of the general public. Such individuals would include representatives from labor, public interest groups, and elected or appointed public health officials.

These suggestions are very similar to those contained in the proposed DHEW regs on health system agencies.

A subcommittee composed of a majority of RAC members who could be said to represent the interests of the general public should be the subcommittee empowered to make recommendations to the Director concerning exceptions to the prohibited experiments, and exemptions from the guidelines.

I will discuss our final two areas of concern, confidentiality and the membership and responsibilities of the institutional biosafety committees simultaneously. One-third of the membership of each IBC should be composed of individuals who have not been affiliated with the institution for at least a year prior to their service on the IBC. At least one of these individuals should be a nondoctoral person from a laboratory technical staff, elected by that nontechnical staff. At least one person

should represent the health department of the local government -- again, selected by that local government. The remainder of the nonaffiliated members should be persons who could be reasonably expected to represent the interests of the community. That, again, is the HSA language.

The membership ratios that EDF suggests are necessary to insure that IBC's will satisfactorily perform their oversight and regulatory roles. It is well known from our sad experience of medical licensing and disciplinary boards, and from the events surrounding the violations of the recombinant DNA guidelines at Harvard Medical School and U.C. San Francisco, that peer review has not provided adequate public protection.

The proposed guidelines' requirement for one nonfacility member does not address this issue sufficiently. There is no provision that this individual at all represent the public interest. It would be very easy for a facility to just appoint another recombinant DNA scientist from a neighboring institution, and yet fulfill the guidelines' requirement for a nonfacility member.

Turning to confidentiality, EDF maintains that all IBC meetings should be announced and open to the public. All MUA's and project registrations from institutions that must comply with the guidelines should also be available to

the public. EDF's reading of applicable statutes, 5 U.S.C. 552 and 18 U.S.C. 1905 indicates that such information submitted to IBC's or to NIH is not exempt from provisions of the Freedom of Information Act. 5 U.S.C. 552 gives NIH the discretion to withhold trade secrets from the public; 18 U.S.C. 1905 provides a criminal penalty for violation of an explicit prohibition against revealing trade secrets or confidential statistical information, but no such explicit prohibition exists in any of the regulations or statutes applicable here. Moreover, the courts have held that the research designs and protocols of noncommercial scientists are not trade secrets, and therefore must be revealed to the public under the Freedom of Information Act.

This decision, Washington Research Project v. DHEW, applies to all recombinant DNA activities, regardless of whether the investigator plans to seek a patent on that research.

In addition, none of the information EDF maintains should be available to the public meets the test for confidential commercial information contained in the National Parks and Conservation Association v. Morton.

EDF maintains that no changes in ongoing recombinant DNA experiments subject to the guidelines should be allowed without NIH approval. The error rate of institutional

biohazard committees has been variously estimated at 4 to 15 percent by NIH's Office of Recombinant DNA Activities. The turn-around time for that office's review of an IBC assessment of containment requirements is only four to five days. For these two reasons, EDF maintains that no changes should be allowed without ORDA approval. And to speed up the turn-around time, EDF suggests that ORDA be given additional staff. There are presently only two people reviewing IBC assessments of containment guidelines.

Finally, EDF suggests that IBC's be required to conduct semi-annual inspections of laboratories engaged in recombinant DNA research and submit such reports of inspections to ORDA and have them publicly available.

Again, this has only been a brief summary of our concerns, and only a brief summary of our thoughts.

Thank you.

MR. LIBASSI: Thank you very much. Any questions from anyone?

Thank you.

The next witness is Dr. June Osborn.

DR. OSBORN: I am June Osborn, and I am a Professor of Medical Microbiology and Pediatrics at the University of Wisconsin at Madison.

My purpose in making a comment concerning the

revised guidelines for recombinant DNA research is to support the general direction of the proposed changes, rather than to comment on specific provisions. I am a pediatrician who specializes in infectious diseases, and also a microbiologist whose primary focus has been mechanisms of pathogenesis of microorganisms. As such, I have been concerned from the outset of the recombinant DNA debate with the relative lack of recourse to the substantial fund of knowledge concerning known pathogenetic mechanisms and genuinely virulent organisms.

The inference has sometimes been that pathogenetic mechanisms of microbes are generally unknown and mysterious, and that once pathogenic, organisms are uniformly so in an all or none fashion. As I read the revised guidelines I was therefore pleased to note that the proposed changes move substantially toward a thoroughly rational, cautious approach to facilitating advances in research under conditions of sensible containment.

Perhaps some consideration of known facts about pathogens will amplify my first point, that the revised guidelines are sensible in their emphasis on the human host, who would be the initial biologic target of an inadvertently released vector. A healthy adult who is not undergoing antimicrobial or immunosuppressive therapy is usually an effective barrier even against pathogenic

organisms that have been millenia in the making. For instance, the meningococcus, which can produce meningitis and/or overwhelming sepsis, is far more commonly carried by a substantial fraction of the population as a harmless component of the throat flora in the winter months. More pertinently, virulent E. coli organisms, not even the weakened strains about which much debate has centered, are poor pathogens at best. And while certain bacterial products made by some strains are thought to augment their potential invasiveness, the vast majority of instances of serious E. coli disease occur in infants or in hosts with immunologic or anatomic predisposition.

My second point is complementary to the first: Even the most virulent of microorganisms has a dosage threshold below which its mechanism of pathogenesis fails. When persons are bitten by a demonstrably rabid wolf, less than half proceed to get rabies, and the presumed reason for the others' failure to become ill is a dosage effect. It has been shown experimentally that 20 million virulent group A streptococci are required in order to establish a pharyngitis in human volunteers; and a million coagulase positive staphylococci can be injected into healthy human skin without causing disease, whereas the presence of an inert foreign body, such as a suture, in that skin suddenly allows 100 staph to establish purulent infection,

again emphasizing the importance of the host's role in successful pathogenesis by microorganisms.

Insofar as mechanisms of pathogenesis are concerned, much again is known about the established pathogens of man. Group A streptococci make M protein which conveys an antiphagocytic resistence to the bearer. Pneumococci make a capsular polysaccharide which serves a similar function. Diphtheria bacilli are entirely innocuous unless they themselves are infested with a lysogenic phage, and even then, proper iron concentrations and other environmental conditions are necessary before toxin production can proceed, and so forth.

It is interesting to note that even in the case of drug resistence, where much of our new infectious disease problems lie, the multiply drug-resistant tubercle bacillus has reduced virulence as a correlative property.

I have conducted this brief exercise in medical microbiology to establish several points: First, that emphasis on the human host working in the environment of potentially new microorganisms is appropriate; second, that dosage is an important element in known pathogenetic microbial disease, and so sensible efforts at containment, with particular attention paid when microorganisms are at high concentrations, can be imposed with a degree of confidence; thirdly, that known, highly virulent pathogens are in

general the product of marvelous evolutionary adaptation which allows them to co-exist in the so-called carrier state far more often than to cause disease in their human host. In this context, parenthetically, the proposal to deal with DNA from viral pathogens at a level no higher than that appropriate to the parent virus seems eminently sensible.

The broader point I would like to make is that biology in general, and infectious disease microbiology in particular, submit to the same rational analysis as do other arenas of science, and while unknowns remain, much hard data and experience can be brought to bear on such discussions as the present consideration of recombinant DNA research.

I therefore want to voice my support for the revision of the guidelines currently proposed.

MR. LIBASSI: Thank you very much. We have no questions.

The next witness is Dr. Harlyn Halvorson.

DR. HALVORSON: My name is Harlyn Halvorson. I am a microbiologist at Brandeis University, and I appear before you today as a member of the Public Affairs Committee and past president of the American Society for Microbiology. This society, ASM, has had a long interest in recombinant DNA research. I cite

three committees that have been involved in this. We had an Ad Hoc Committee that reviewed the initial guidelines, with continued reviewing and contributing to this process; a Public Affairs Committee which, together with other scientific societies, has tried to develop consensus positions regarding regulation of the research; and a Working Panel that is involved in trying to recommend training procedures for conducting recombinant research. In addition, we have solicited widely to have our members give their views.

I have submitted some details of this in a letter to Dr. Fredrickson which, with your permission, we hope will be part of the record.

What I would like to do today is to concentrate on five separate topics that reflect in part the consensus we have established with other scientific societies.

First, regarding development of the guidelines themselves, in testimony before congressional committees we have argued that the guidelines as periodically reviewed are appropriate for governing research on recombinant DNA. We believe that the experience of the last few years justifies this approach. We applaud the excellent job that the Director and his staff at NIH and the Recombinant DNA Advisory Committee have done in developing the revised guidelines.

We also endorse the conclusion of representatives of critical disciplines in epideniology, infectious disease, medical microbiology, and virology as advisors. Their expertise and the workshops such as the Falmouth meeting, the Ascot meeting, and the workshop in Washington on Risk Assessment of Agricultural Pathogens provide, we believe, essential, valuable information for this process.

We believe that such an approach is sound, and it increases the confidence and quality of decision-making. New hosts and vectors in recombinant DNA research are to be expected, and the procedures for evaluating them or assigning then appropriate containment levels have been developed, we believe, by NIH.

The second area deals with changes in containment levels. During the last two years there have been dramatic contributions on DNA recombinant research, as we are all aware. And concern over the freedom of research and protection of the public in such a rapidly changing field will continue to be characteristic of this area.

We support the approach by NIH to continue to review the risk-assessment data of host-vector systems to provide conservative guidelines. The lowering of containment levels for recombinant DNA research based on viral vectors following the detailed evaluation experience with animal viruses -- the ESCO meeting and the Ginsberg report -

represent the type of public responsibility in evaluating risk experiments which we think should serve as a model for other host-vector systems. The resulting reductions in containment levels, in our opinion, are justified and are based on sound principles of pathogenicity and epidemiology.

We recommend that in the continuing process of risk assessment that the appropriate experts as committee members or ad hoc committees be employed and that their evaluations continue to be exposed to public scrutiny. The use of workshops, special studies, open, publicized meetings of the Advisory Committee are sound and appropriate procedures to evaluate containment levels.

The third area deals with the responsibility of the institutional biosafety committee. In testimony last year before the Kennedy Subcommittee, we suggested that the IBC should have a leading role in assessing individual laboratories as to the adequacy of safety procedures and appropriate levels of physical containment, biological containment, provision of educational materials, and the review of experimental design.

We support these developments in the revised guidelines, and reiterate that the local groups are more knowledgeable of the strengths and weaknesses of any scientific colleague than is possible frequently with a

governmental review agency. This procedure has a proven history in protecting human subjects in medical centers.

Increased authority to the IBC carries with it the responsibility of assuring that this committee has the relevant scientific expertise and public -- that is, non-institutional -- representation. We suggest that the NIH Advisory Committee may want to consider in its further development of policies, recommendations on the composition of IBC's to ensure that it is capable of fulfilling this responsibility. As we pointed out in the Stevenson hearings, the above recommendation carries with it an obligation of NIH to bear some of the financial costs for appropriately transferring federal responsibility to IBC's.

The fourth point deals with the authority of the Director to make exceptions. We are firmly convinced that it is essential to continue to provide authority to the Director of NIH, with appropriate study review, to make exceptions to the guidelines. First, experience has shown that this authority is exercised with care and only after careful review. Second, after the initial guidelines, one cannot anticipate all the advances and opportunities and new information on natural gene transfers or risk assessments. For example, it is not unlikely that Bacillus punulis and Bacillus subtilis may exchange genetic information naturally. If this could be demonstrated such recombinant DNA

experiments should be permitted. Thirdly, there are a series of experiments which should be conducted under highly controlled P4 conditions. Recombinant research with Class 3 etiological agents are not permitted, in spite of a need to explain basic mechanisms of pathogenicity with these agents, and in spite of the existence of a national P4 facility.

Our greatest need is for good risk analysis, particularly with Class 3 organisms, in which knowledge of genetic systems is scanty, and where our own need to develop defense mechanisms is the greatest. The need, for example, to conduct the risk assessments Dr. Wally Rowe carried out with polyoma virus, with wild type E. coli is essential in developing national policy. Thus, we believe it is important that the Director have such authority, following proper review and availability of a P4 facility, to permit such types of experiments.

The final area deals with roles and responsibilities. This issue concerns the assignment of responsibility. For the past two years we have supported the view that substantial responsibility be transferred to IBC's. We approve of the recommendations in Section IV of the guidelines to implement this goal. We are convinced that license revocation and the witholding of federal funds are both sufficient and effective restraints to effect

compliance with the guidelines. Research in the private sector is not covered by the guidelines, and can only be governed by legislation. We note that PMA and individual company representatives have committed their organizations to volunteer compliance with the federal guidelines.

While supporting the present proposed guidelines, we are concerned that NIH retain surveillance over local biosafety committees. It is important that NIH have the authority to assure uniform, national standards of compliance with these guidelines. In the absence of overriding federal legislation, the steps defined in the July 28, 1978 guidelines represent an acceptable interim procedure.

Thank you.

MR. LIBASSI: Thank you very much.

I would like to call as the next witness Congressman Ottinger, who has limited time. So we would like to interrupt the list of speakers and call on him next.

Thank you, Congressman Ottinger.

MR. OTTINGER: Thank you very much, Mr. Chairman and members of the Panel. I appreciate you giving me this opportunity to appear before you this morning. I will be brief.

I would just like to make a few remarks this morning about the urgency with which I am convinced HEW

must act to regulate recombinant DNA research. As the first member of Congress to have introduced legislation on this matter nearly two years ago, probably the most far-reaching legislation that was introduced, I have watched with escalating concern the increase in commitments, particularly in the commercial sector, to recombinant DNA research.

Quite simply, the whole matter is rapidly getting out of control, and it is at this juncture appropriate for HEW to take the reins and protect the public from any further loss of control until Congress acts.

The failure of Congress to act is one which deeply troubles me, and I am personally very disappointed, as I know is Chairman Rogers, the Chairman of the Health and Environment Subcommittee on which I serve. But that failure is not one upon which HEW should now base any excuses for inaction. Rather, it is directly because Congress has not acted and cannot act during this session, that I come before you today to urge that you act.

The failure of the Congress resulted from some of the most vigorous, and in many instances distasteful, lobbying I have ever seen on any issue. When the scientific community establishment gangs up on Congress saying that its expertise is absolute, and that there is no other recourse for protecting the public, it seems clear that

Congress is hard-pressed to resist.

I personally got calls from the heads of three of our major universities, from the heads of some of the giant corporations of America on this issue, an effort which seemed to me far out of proportion to the problems that would be caused to them by regulation.

On the other hand, we heard testimony from some of the most eminent scientists in the country and in the world, who testified that there were potential dangers of very grave magnitude if we didn't properly control some of the DNA recombinant research.

It has the potential for bringing us some very great benefits, but also perhaps some of the greatest horror stories since we dropped the atomic bomb in Japan. And indeed, the former head of New York's Cornell University described the potential of DNA recombinant research to me in precisely those terms.

The recent transport of smallpox from England to the United States is illustrative of the kind of problem we might face with DNA recombinant research. We were told a year ago by the World Health Organization that smallpox had been eradicated, and was only a concern for historians. It is now clear that such optimism was premature. While smallpox may have been confined to the laboratories, mostly for archival purposes, the threat to public health was

unfortunately not entirely eliminated. The virus in England escaped through a so-called faulty filter, and contaminated workers in and around the laboratory in Birmingham University. A medical photographer fell victim to this virus and died. The director of the laboratory committed suicide. The threat from this outbreak even spread to the United States, when an individual exposed in England flew to North Dakota.

This episode with smallpox parallels and highlights several concerns about research in the area of genetic manipulation. First, labs cannot provide foolproof containment of dangerous organisms. From the testimony we received as to the very sloppy procedures with respect to safety that occur in many laboratories, it is quite evident that surveillance and standards are highly necessary.

Biohazard outbreak, secondly, unlike any other type of threat, can rapidly spread to virtually any neighborhood on earth.

And third, the more over-optimistic the picture painted by the scientific community, the more vulnerable the public is to health disasters, especially from unprecedented genetically-hybrid forms, against which nature may have evolved no immune mechanisms.

I realize that stringent standards on this

type of research may be expensive, and may have some inhibiting effect on the progress of research. We were told, however, that DNA recombinant research was merely one tool for reaching these answers, and that there are other available tools for virtually every kind of research being conducted.

We treat these hazards very much at our peril. I strongly urge HEW to act, to reduce their guidelines to regulations, and to the extent that the law permits, to extend that to the private sector. I would urge that you act under Section 361 of the Public Health Service Act. It may not be the perfect instrument, but at least it provides, I think, sufficient authority for your action.

I do wish I could assure you that Congress would quickly provide you with more precise authority, but unfortunately, I cannot. Even if we were to act early next year, and that is doubtful, it would take an additional year to prepare regulations. In my opinion we can't afford to wait any longer. Imperfect as the world is, and as imperfect as Section 361 may be, waiting is only going to make matters worse. And were there to be an outbreak of diseases caused by DNA recombinant research, and some new organism that escapes from a laboratory, then I think that the embarrassment to HEW, and the Congress as well, would be very great. The

dangers to which people would be exposed unnecessarily would be highly unfortunate.

So I do hope that you will use and stretch the existing authorities that you have to the maximum, and issue regulations on this subject at the earliest possible time. I will thank you again for the opportunity to appear.

MR. LIBASSI: Thank you very much, Congressman.

The next witness is Dr. William Whelan.

DR. WHELAN: My name is William Whelan. I am a biochemist from the University of Miami School of Medicine, and I am the Chairman of the Committee on Genetic Experimentation of the International Council of Scientific Unions. That Council is an international, nongovernmental scientific organization of 18 autonomous international unions, scientific unions, with more than 60 national members made up from academies of science.

COGENE, as this committee is called, came into being in 1977. It is supported by seven of the member unions, and a number of scientists prominent in the field of recombinant DNA research are members of it. I, as the chairman, and also the secretary, am not engaged in this research.

The members of COGENE and its working group come from 13 of the major nations in which this research is being carried out, and we also have affiliates from intergovernmental

major organizations, such as the United Nations, UNESCO, and FAO.

The terms of reference of COGENE are that it should serve as a nongovernmental interdisciplinary and international council of scientists and as a source of advice for governments, intergovernmental agencies, scientific groups and individuals concerning recombinant DNA activities. COGENE's activities are being conducted through working groups, and it is the reports of two of these working groups that I would like to summarize for you today. One of these has reached printed form, and will be presented to ICSU next week. The other one has been written especially for this meeting.

Those working groups are one on guidelines for research on recombinant DNA, of which the convener is Stanley Cohen from the United States, assisted by scientists from Canada, Australia, the Soviet Union, France the Federal Republic of Germany, and the European Molecular Biology Organization. The second one concerns risk assessment experiments, and the convener of that is Dr. Ann Skalka, from the United States, who is here today, assisted by Dr. Bernardi from France and Dr. Sgaramella from Italy.

The Working Group on Recombinant DNA Guidelines was established last year and charged with the responsibility

first of all, of obtaining information about the status and content of recombinant DNA guidelines in different nations, and secondly, analyzing, comparing and evaluating the provisions of the various national guidelines, and the premises on which these provisions are based.

At the end of March, 1978, at least 367 Recombinant DNA projects were estimated to be underway in 155 laboratories in 15 countries. Seventeen nations have drawn up guidelines for recombinant DNA experimentation and these were in force in 13 nations. Five of the nations had prepared their own guidelines, whereas the rest had adopted or modified guidelines of the United States or the United Kingdom.

Of the responding nations that had not drafted guidelines by the time of the response 13 intended to do so, while four indicated no intention to establish guidelines. Sixteen recombinant DNA projects were indicated as being underway in nations where no guidelines existed.

The Working Group's analysis of the various national guidelines under the responses to their questionnaires, has led to the following preliminary conclusions: First, during the past several years guidelines for the conduct of recombinant DNA experiments have been prepared by a number of nations whose national scientific bodies are members of the International Council of

Scientific Unions. Some nations carrying out recombinant DNA experimentation have not promulgated formal guidelines, and some do not intend to do so.

Two, guidelines of most nations have been derived directly or indirectly from those of the United States, which were the first to be promulgated, and the assumptions implicit or explicit in the United States' guidelines have been incorporated in guidelines of other nations. Although fine gradations of risk and containment are specified in most national guidelines, the basis for such distinctions appears to be entirely conjectural. No documentation to support the assumption of risk is provided in any of the guidelines examined.

While the guidelines of other nations have been generally patterned after those of the United States, there are substantial differences in the various national guidelines. Some have the force of regulations, while others are considered simply a standard operating procedure, and their procedures and their observances voluntary. Some guidelines are concerned only with organisms containing recombinant DNA molecules, while others also pertain to the recombinant DNA itself. Some have employed an encyclopedic approach which attempts to anticipate and specify conditions for all possible forms of recombinant DNA experimentation, while others have adopted an approach

that utilizes a case-by-case analysis for determining the containment necessary for a particular kind of experiment.

Number four, identical experiments require strikingly different levels of precautions in different nations. Moreover, although the general approach to biological and physical containment first proposed in the U.S. guidelines has been adopted by most other nations, the specific characteristics of each containment level differ markedly among different nations.

Five, in some nations the guidelines specify the maximum level of precaution required, and the national committee may reduce precautions from this level under certain circumstances. In other nations the guidelines specify the minimum level of protection required, and precautions may be increased by the actions of local or sub-national bodies.

Six, those guidelines that have been prepared more recently are, in general, less restrictive than the earlier guidelines. This appears to reflect a changing assessment of the risk of recombinant DNA experiments as greater experience in this area of research is accumulated. However, the guidelines of most nations do not have a time limitation clause, and the frequency of revision of guidelines is usually not specified.

Seven, the various national guidelines appear

to be intended to deal with the risk of major epidemic, although the chances of initiating an epidemic by recombinant DNA experimentation in E. coli K12 or analogous nonpathogenic organisms, appears negligible.

Eight, the level of containment required for work with recombinant DNA from known pathogens is often greater than that specified for work with the enteric pathogenic organism. The guidelines of some nations effectively prohibit recombinant DNA work with genes from medically important disease-producing organisms, although recombinant DNA methods appear to provide the means of carrying out such studies at less risk than is involved in the work with the pathogens themselves.

Finally, the status of guidelines for recombinant DNA experimentation is undergoing rapid change at this time. This appears to be the result of a changing assessment of the conjectural risks that led to the initial formation of guidelines, and regulations for research in this area, and the realization of substantial benefits from the use of this research too.

The summary of the Working Group on Risk Assessment reads as follows: "The Working Group has been charged with the task of gathering information related to an assessment of risks associated with recombinant DNA research. The concerns regarding recombinant DNA research

can be summarized as follows: One, organisms containing recombinant DNA may spread in the natural environment, and disrupt existing ecological equillibria. Two, the organisms might produce some toxic or noxious substance or otherwise cause disease. Three, by exploiting this technology, scientists may be crossing some hypothetical barrier to DNA exchange between eukaryotes and prokaryotes, and thus affect pathogenicity or dispersion of pathological agents.

"Reports from the Falmouth meeting, and COGENE-sponsored analyses of E. coli K12 systems show that many relevant experiments have already been conducted by scientists in such closely related fields as epidemiology and infectious diseases. The observation that E. coli K12 has a limited prospect of survival and the consensus that this bacterium cannot be converted into an epidemic pathogen by laboratory manipulations with DNA inserts do much to satisfy the first concern mentioned above.

"In addition, long-term monitoring of laboratory workers who routinely handle K12 organisms carrying transmission proficient plasmids showed no bowel colonization despite the fact that the work was carried out without any special precautions.

"If the organisms which carry recombinant DNA

could not spread in a natural environment, then clearly the other concerns are also diminished.

"The conclusion of the Virology Workshop was that recombinant DNA organisms carrying viral inserts cannot be any more hazardous than the viruses themselves, and in some instances may provide an opportunity to work more safely with virulent agents.

"Replies to our surveys indicate that there are several projects currently underway directed specifically toward risk assessment. Preliminary results as well as conclusions from the NIH/EMBO Virology Workshop indicate that these studies are unlikely to reveal unknown hazards.

"In summary, our analyses have revealed no scientific findings to justify any of the three concerns listed above. No risk unique to recombinant DNA has been identified. Available evidence indicates that recombinations of the type made possible by this new technology can occur in nature. Evaluation of E. coli K12 shows that this bacterium is essentially harmless, and that insertions of segments of foreign DNA into its genome cannot alter this property. With few exceptions, it seems likely that the same will prove true of other host bacteria.

"These conclusions cannot be ignored if the guidelines governing recombinant DNA research are to

remain rational and useful."

MR. LIBASSI: Thank you very much.

Let me call Dr. Faust from the Department of Agriculture as the next witness.

Incidentally, let me just say that while one member of another Federal department is speaking now, I do want to acknowledge the cooperation of the Federal Interagency Committee, which has been working with Dr. Fredrickson on these guidelines for some time -- several months, or in fact, more like several years. We do appreciate the cooperation which the other Federal agencies have been giving to us.

Now, I think if we are ready, you may go ahead, Dr. Faust, from the Department of Agriculture.

DR. FAUST: I am Robert Faust with the Department of Agriculture's Research Center in Beltsville, Maryland. I am also the chairman of the biosafety committee there at that institution.

In October of 1977, the ARPAC Subcommittee on agricultural recombinant DNA research was established to concern itself with matters relating to guidelines for recombinant DNA research and any regulatory processes that might develop. It also was assigned the responsibility for developing recommendations and possible model procedures indicating how agriculturally related sciences and their

sponsoring organizations should be moving forward to conduct recombinant DNA research, identify and share beneficial findings, and also safe applications of such findings.

The Committee responded to the USDA's "Notice Regarding Research Involving Recombinant DNA Molecules," which purpose was to state USDA policy with respect to the administration and conducting of research involving recombinant DNA.

We recommended that the Joint Council on Food and Agricultural Sciences develop standardized procedures for extramural and intramural recombinant DNA research to assure that the same guidelines were being followed and honored; that the "Notice Regarding Research Involving Recombinant DNA Molecules," developed by the USDA Recombinant DNA Committee, be accepted that wherever feasible, scientists working on recombinant DNA should be governed by a local biosafety committee, regardless of the source of funds, and that the conditions for performing recombinant DNA research, as published in the Federal Register in June 1976, be adopted as USDA policy and adhered to by researchers for which USDA funds are used, either intramurally or extramurally, or through grants, contracts, and cooperative agreements.

Although the committee recommended the adoption

of the NIH guidelines as a part of USDA policy, members of the committee did express their concern for the extremely restrictive nature of the 1976 guidelines that particularly impeded the application of recombinant DNA technology in agriculture for such projects as genetic improvement of food and fiber crops and the development of more useful and reliable biological insect control agents such as the baculoviruses and entomopathogenic bacteria in lieu of certain hazardous chemical insecticides.

We are generally satisfied with the considerations that the NIH has given and incorporated into the revised guidelines, especially for those major suggestions for revision that were made to NIH as a result of the Airlie House meeting and the workshop on Risk Assessment of Agricultural Pathogens.

We further note, with satisfaction, NIH's attempt to meet the concerns of agricultural scientists regarding the easing of restrictions for recombinant DNA research with plants, non-primate vertebrates, and invertebrates, and regarding the release of recombinant DNA-containing organisms into the environment.

Although the NIH has incorporated a statement to the effect that the prohibition of deliberate release into the environment of recombinant DNA-containing

organisms can be waived if all of the requirements for waiver are met, we would like to reemphasize it is obligatory that the U.S. Department of Agriculture be deeply involved in this process. Our main concern with this item resides in the mechanism of waiver, the definitive requirements for a waiver, and the latitude that the waiver requires for release. We would encourage the NIH to draw upon their resources, such as the USDA, OSHA, and the Environmental Protection Agency in order to furnish researchers more definitive guidelines for the waiver.

There have been some suggestions made that the institutional biosafety committees are self-serving, ineffective, and in reality are only researchers regulating themselves. As chairman of the Beltsville Agricultural Research Center Biosafety Committee, I take exception to this suggestion. The membership of our committee was purposely made diverse, and includes, one, individuals from a number of scientific disciplines -- those that have interest in recombinant DNA and those that do not; two, individuals who are knowledgeable about laboratory safety and engineering principles; and three, laboratory technical staff.

Our first recombinant DNA project submitted for certification to the committee was in fact returned

twice for further elaboration before complete approval by the membership was given.

Committee members recognize that such research may involve biohazards and are mindful of the public concern on recombinant DNA. Further, it is well recognized that it is essential that all research involving the use of recombinant DNA molecules be conducted in a responsible manner, adhering to safety precautions and conditions designed to protect laboratory workers, the general public, and our environment.

Earlier this year, I had the opportunity to attend a biosafety committee meeting at the Scripps Clinic and Research Foundation at La Jolla, California. The Scripps biosafety committee had a similar profile, and was extremely effective and nonpartial in their deliberations. I am certain, without reservation, that institutional biosafety committees can be relied upon for authoritative and proper implementation of the guidelines, provided those committees are required to be organized and established according to the recommendations of the NIH.

Lastly, some questions have arisen at the Agricultural Research Center concerning certain interpretations of the revised guidelines that relate to specific scientific and research containment procedures and

requirements. The possibility of using recombinant DNA procedures for the development or improvement of entomopathogenic strains of bacteria for insect management has been considered by myself, and I have begun some of the basic research necessary to facilitate the use of bacteria towards this end. Envisioned are possible applications of *in vitro* gene-splicing and recombinant-DNA-cloning to, one, expand the insect-pest host spectrum of existing insect pathogens; two, develop more potent strains of pest insect pathogens; three, improve the physiological tolerance and epidemiological properties of these bacteria; and four, facilitate the *in vitro* commercial production of the more fastidious insect pathogens by expanding the range of substrates upon which they can grow. Two of the present organisms with which I am working, *Bacillus popilliae*, the Japanese beetle pathogen, and *Bacillus thuringiensis*, a pathogen of pest caterpillar larvae, both enjoy EPA registration and exemption from tolerance in the environment.

Back in October of 1977, a copy of my proposed recombinant DNA program was forwarded to the NIH Office of Recombinant DNA Activities for comment and clarification of certain aspects of the 1976 NIH guidelines dealing with shotgun experiments in prokaryotes. Apparently the NIH Recombinant DNA Advisory Committee was unable to come to

a definitive decision on the proper containment levels, for in April 1978 I received a letter from William Gartland, Director, suggesting that I submit a draft statement for consideration by ORDA on the containment levels of recombinant DNA research with entomopathogenic bacteria that have EPA registration. On April 24, 1978, I submitted such a statement as required.

Although the proposed revised guidelines will simplify the problem of this interpretation, there is still left a rather bothersome issue that is also found in other sections of the guidelines. Under Section III-B, "Experiments with Other Prokaryotic Host-Vectors," host-vector systems which have been approved as HV1 systems may be used under P2 containment conditions for shotgun experiments with phages, plasmids, and DNA from nonpathogenic prokaryotes which do not produce polypeptide toxins. Therein is the quandry. Both of the proposed organisms for recombinant DNA research are pathogenic, but only to target insects, and one of them, Bacillus thuringiensis, produces a polypeptide toxin which is the basis of its pathogenicity. The toxin, however, is only specific for certain insects, and has been demonstrated ineffective against other life forms, including man.

I would respectfully request that the NIH define more concisely the nature of the pathogenicity

and the types of polypeptide toxins meant in the revised guidelines. That is to say, pathogenic and/or toxic to what life forms?

Further, the investigator is hard pressed to analyze the biological containment requirements for such experiments. Can an organism that grows in an insect or is found as a common soil organism, but only affects specific insects, be developed for pest control use and be considered an HV1 system for shotgun experiments using DNA from entomopathogenic bacteria? The revised guidelines apparently do not address such types of bacterial recombinant DNA experiments.

We further would ask the NIH to consider that the entomopathogenic bacteria or the baculoviruses be only required to meet the criteria of EPA for an exemption from a requirement of tolerance, which verifies that the organism has been rigorously tested for safety to mammals and other nontarget organisms in the environment, rather than have EPA registration stipulated for placement in a specific containment level. Registration of the organism is granted subsequent to the exemption from a requirement of tolerance, provided the organism is shown to be efficacious.

Section III-C-3, "Plant Viral Host-Vector Systems," dealing with DNA plant viruses serving as vectors for cloning

genes in plants, we question the statement, "the plants should be grown under P1 conditions -- that is, in either a limited-access greenhouse or plant-growth cabinet which is insect-proof." Rather than insect-proof, perhaps the NIH means insect-restrictive, since insect-proofing infers a facility greater than P1 as recommended. We believe it is virtually impossible to have a P1 facility that is insect-proof and still remain classified as P1.

Thank you.

MR. LIBASSI: Thank you, Dr. Faust.

Would you have extra copies of your extended comments?

DR. FAUST: I gave five copies of the summary and the statement to the staff.

MR. LIBASSI: Where individuals are submitting summaries of their statement, but have a longer statement, be sure that we get both your summary and your longer statement. We would like to not have to wait for the transcript in order to begin going through the full statements.

Now, Dr. Dhun Patel is next.

DR. PATEL: Mr. Chairman, Committee members, ladies and gentlemen, on behalf of the Department of Health and the Public Health Council of the State of New Jersey, we are in full support of the efforts of

the National Institutes of Health, the scientific community, and public interest groups which have enabled the development of guidelines on recombinant DNA research. In order that they may have full impact, our comments today will be brief.

In the State of New Jersey, we are concerned about the conduct of research at all institutions which have ongoing projects or are planning projects involving recombinant DNA. In particular, we are concerned about research at those institutions which do not receive NIH funds and are not subject to the NIH guidelines. Therefore, we strongly urge you to retain in the final version Sections IV-C-2, IV-C-3, and IV-C-4 of the NIH revised Guidelines, as appearing in the Federal Register of Friday, July 28, 1978. These sections are entitled, "Voluntary Registration and Certification," "Disclosure of Information," and "Patentable Materials."

In essence, by retaining these sections, any institution which is not covered by the guidelines will be permitted to register their recombinant DNA research projects with NIH, and can request certification of proposed host-vector systems by NIH. The registrants will then in turn be required to abide by the physical and biological containment standards of the NIH guidelines.

As you know, review of project proposals and

certification of host-vector systems require enormous resources, both in terms of scientific personnel and finances. Thus, it would place a heavy burden on any State government if NIH decides not to retain the above-cited sections of the NIH-revised guidelines.

Retention of the section which will permit all institutions to register recombinant DNA research with NIH should also allay industry's concern regarding disclosure of proprietary and patentable information, since one governmental agency only would receive such confidential information. As an additional benefit, retention of this section will provide the private sector an opportunity to demonstrate their social responsibility and enhance public credibility.

Another area of concern to us at the State level is that of major spills or transportation accidents of such etiologic agents. As referred to on page 33067 of the Federal Register, a team of experts from NIH and CDC could be formed to respond to emergencies of this nature. However, we feel that for a prompt and adequate response it is essential that such a team be in existence, and the names and telephone numbers of such a team be published in the guidelines for easy access in an emergency. We also need more than one team for the different regions of

the country. Furthermore, the guidelines should stipulate that some State agency, such as the health department, be notified immediately in the case of any accidents.

Finally, in order to keep the State agencies informed of any noncompliance with the Guidelines, we propose the following wording: "and responsible State agencies" be added to part IV-B-3-a-(4) of the Guidelines so that it will read as follows: "Provide timely notice to local institutions and responsible State agencies when protocols, including modifications to ongoing projects, do not conform to the standards in the NIH Guidelines."

Thank you for the opportunity to present this statement at today's hearing.

MR. LIBASSI: Thank you very much, Dr. Patel.

Mr. Bereano?

MR. BEREANO: Mr. Chairman, I have submitted several copies of my extended remarks. I hope the panel has them. At any rate, I have more if you need them.

MR. LIBASSI: I think we do have them.

MR. BEREANO: Okay, fine.

MR. LIBASSI: Thank you.

MR. BEREANO: My name is Philip Bereano. I am an Associate Professor in the Program in Social Mangement of Technology at the University of Washington in Seattle.

My academic training has been in chemical engineering, law, and planning. I am a member of the New York Bar, and a former Commissioned Officer in the Public Health Service. For eight years I have been doing university teaching and research in the areas of science, technology and public policy, first at Cornell and now at the University of Washington. I have been a member of the University of Washington's institutional biohazards committee since its inception.

Today I wish to comment on the public policy aspects of the proposed revised guidelines, and my testimony is being submitted on behalf of the Coalition for Responsible Genetic Research. I will be directing most of my comments to the section on Roles and Responsibilities of the proposed guidelines.

In a commencement address at the University of Michigan in 1977, Secretary Califano pointed out that science has become too important to be left solely to the scientists. With specific reference to recombinant DNA research, he noted that policy deliberations in this area must be conducted with concern and deliberation. And he said, "This is the slowest way, the most inconvenient way, and in a democracy, the only way to make such decisions." He went on to observe that decision-makers in science and medicine must learn the

hard lesson that decision-making behind closed doors breeds distrust, even if what happens, in terms of the actual outcomes of those decisions, is legitimate.

I have some concerns with the guidelines as published, although there are aspects of them which are praiseworthy. I will concentrate on some of my concerns in order to maximize my contribution to your deliberations.

My work in such areas as technology assessment over the past number of years has led me to understand that one of the most fundamental sets of questions that needs to be asked when considering new scientific and technological development concerns not only the attempt to anticipate probable future consequences of such an activity, but to disaggregate those consequences by asking who actually would be bearing the risks associated with new developments? Who would be paying the costs of those developments, and who would have access to the potential benefit?

In regard to work in the area of recombinant DNA, it is clear to me that members of the general public fall into all three categories. Much, if not most of this research is supported by tax dollars paid by the general citizenry. Risks to health, safety and environment would be widely shared. And benefits which

have been suggested for such research would affect many sectors of society.

Thus, I believe that members of the general citizenry have a fundamental right to participate in policy-making and decision-making which goes on in regard to recombinant DNA research. One of the problems I have with the guidelines is that I don't think they make adequate provision for this.

As a matter of fact, I can say quite clearly that were the IBC at the University of Washington to follow the model suggested by the guidelines, I think that our activities would be severely restricted compared to what we do now, that it would be a substantial setback in the efficiency of our work and the confidence with which we are held by members of the general public.

Among my remarks today, I want to talk a little bit about the notions of risk and safety, mainly because I think that they are very important in this whole regulation of recombinant DNA, and because I think the guidelines confuse the two concepts, and are not helpful to the IBC's and to the general public in sorting this out.

The distinctions between risk and safety have been set out in the literature. For example a recent book, "Of Acceptable Risk," by William Lowrence, who is

presently a Special Assistant to the Undersecretary of State for Security Assistance, Science and Technology, and who was a participant in the March 1977 Academy of Sciences Recombinant DNA Forum.

Risk is a relatively objective determination of the probability of something coming about. Safety is a much more subjective blending of notions of risk with what is deemed acceptable by the population which would have to bear the risk. In other words, even if the various risks associated with DNA experimentation can be determined once and for all by an authoritative body, the question of safety involves many value issues which can only be articulated and developed by those members of the public which might be exposed to such risks, and have the potential of access to the benefit of the activity.

None of us lives in a risk-free society, but all of us in our everyday life have to cope with notions of risk, and I think in effect the NIH begins to recognize in the guidelines some of these concepts. And I am referring also to the laboratory safety monograph. But I don't think, as I said, that there is a clear distinction between risk and safety. For instance, on page 33084 of the regulations, there is a statement that safety involving recombinant DNA molecules depends primarily on the

individuals conducting the research activities. What the revised guidelines apparently mean is that the risks involving recombinant DNA research depend on the individuals conducting the research, and the manner in which they conduct it.

But safety is not the province of the researchers alone. It is the concern of the larger community; and in its determination the researchers have an important role to play -- that is, the provision of factual information; but the local public is the one to bring the values and make the determination as to what risks are deemed acceptable.

I have a problem in that regard with the comment in the guidelines that the motivation and good judgment on the part of the researchers are the keys to protecting the health and environment. I think that the value issues raised by that kind of approach are quite serious.

Basically I guess what I want to say is that I think, today, largely the regulation of recombinant DNA research has relied too heavily on an old-boy network, and I think that this is perpetuated by the provisions which would regard, for example, the composition of the institutional biohazard committees.

I think that it is very significant, if not the most significant aspect of the new guidelines, that they would delegate a large measure of responsibility to the

IBC's from the NIH itself, and I think that the provisions for the composition and the competence of those committees are completely inadequate to carry out those new responsibilities.

Now, others here today will testify about some preliminary research that I have been engaged in with them having to do with the composition of IBC's at present. Let me just state, though, briefly, that they are hopelessly skewed demographically. They are not at all representative of the populations at risk or the people paying the costs, nor of the groups which might reap the benefits of this research, and I think, therefore, not a good model to follow.

The guidelines would perpetuate this kind of situation. For example, they require that a member be from a discipline such as engineering, but not from the policy sciences. They only recommend that certain categories of persons be on the committees.

I agree completely with comments of some of the earlier speakers that the provision for one non-institutional member could be easily circumvented in terms of having representation by the public. The guidelines should clearly mandate public membership -- membership by people reflecting community groups and individual citizens on the IBC's.

I will talk a little bit about my opinions on the

delegation of authority in the guidelines, because as I say, I feel this is quite significant.

The response of the NIH in the guideline revisions, I believe, has been to propose to enhance the responsibilities of local institutions rather than to make sure that there is a balance or safeguard against some of the kinds of irresponsibility which have occurred in the past. At this time I do not believe that sweeping delegation of authority for initial approved experiments should be made to the IBC's, both because they are unrepresentative, and because, as I hope I have time to point out, in many ways they are not going to be competent as envisioned in the guidelines, to carry out the responsibilities envisioned for them.

For example -- to skip ahead briefly -- most IBC's are composed of people who are donating a little bit of their time, part-time, a couple of hours a month, to this activity; and no one, except perhaps actual DNA researchers themselves, have the time, or energy or competence, to actually inspect the laboratories, or to monitor on any systematic basis the standards of care that are followed there.

This is a free kind of donation of services on the part of most people who hold other jobs and have other demanding responsibilities to family and to community, as well as to professions. But the whole question of the most

appropriate bounds of authority between a central federal agency, which could assure that requisite technical and policy considerations are brought to bear on aspects of the regulatory process, and the local IBC's, which could assure sensitivity to local conditions and provide an extended means of public participation in the regulatory process, needs to be further developed.

My written comments expand on this a bit. Let me point out that one of the problems with the guidelines as written is that they amount to what I would call paper platitudes. That is to say, nice things are written down on paper, but there is no assurance that those things can be translated into actual practice of what goes on in the laboratories. I have had students of mine who have gone into P2 laboratories and found people eating lunch there, although they are not supposed to. It is not because they are mean or evil researchers, it is because of the fact that human beings are careless and become irresponsible. Those are the kinds of things that need to be protected against.

I have a set of procedural requirements I would like to recommend to the committee. They are ones that we use at the University of Washington, in our IBC. They are quite sensible, and I think they

should be mandated. For example, all of our meetings except for the actual voting on research proposals are open to the public. Not only that, but every researcher must prepare a summary in lay language of the proposal, or else have that available for distribution to the members of the public who come to the meetings, to answer questions and the like.

MR. LIBASSI: Your time is up. Your comments appear in full in your statement?

MR. BEREANO: Yes.

MR. LIBASSI: All right, thank you very much. We will consider those.

MR. BEREANO: Thank you.

MR. LIBASSI: Next is Deborah Feinberg.

MS. FEINBERG: My name is Deborah Feinberg, and I an an environmental scientist for the New York State Attorney General's Office. In the interest of time I will only touch upon some of the comments in my prepared statement, but I would like to submit it in full, and I have copies available. I will leave them on the desk in the back, okay?

My office has been closely involved in the recombinant DNA issue. We held a public hearing on biohazards, issued an Office Report, issued comments on the Environmental Impact Statement, and drafted

legislation, passed this spring, to regulate recombinant DNA research in New York State. I have copies of that legislation also, if anybody is interested.

The proposed guidelines under discussion today constitute a substantial downgrading in containment from the original NIH guidelines. My office believes that this reduction in containment levels is not warranted by scientific evidence, and is not in the public interest. That we have not as yet experienced any disease outbreak resulting from recombinant DNA activities is not proof of safety. There are no substantial facts or data to allay the fears of potential dangers which initially prompted the guidelines.

We recommend that the original guidelines remain in effect. Among the areas that trouble us are the following: The proposed guidelines do not adequately take into account ecological impacts. A great deal of concern has been expressed over the possibility of creating an epidemic while the more likely possibility of inadvertently disrupting the ecological balance has been overlooked. A recombinant organism need not only produce a pathogen to cause harm. If an organism gains a slight competitive advantage by producing more of an enzyme than does the wild type, it could conceivably alter the balance of an ecological system with grave

consequences. We can have no assurances of safety until we understand how an organism will interact in a complex ecological situation.

The proposed revised guidelines exempt from compliance non-novel exchanges. The rationale behind this exemption is that such exchanges take place in an unregulated manner in nature. We have two objections to this exempt category. First, the exemption list is too broad. Given that one member of the genus is known to exchange genetic material with an unrelated species in nature we should not extrapolate that all members of that genus should be exempt. We must ask whether other members of that genus would meet this organism in a natural setting.

Second, the rationale for these exemptions ignores basic ecological considerations, such as natural rates of exchange and the effects of concentrated products of such non-novel exchanges in the environment. If one piece of DNA is exchanged naturally, that does not mean that the transfer of any segment of DNA from that organism is safe. Similarly, if the organisms exchange DNA in a limited manner, increasing the rate of exchange could result in the concentration of an enzyme or hormone within an organism with unknown results. In the laboratory we do not reproduce natural

conditions. We place organisms together that might only rarely find themselves in close proximity in nature. Until we can anticipate the results of altering an established ecological balance, such experiments should not be exempted from the guidelines. This same consideration applies to self-cloning experiments.

The proposed revised guidelines also exempt recombinant DNA experiments using naked DNA on the grounds that it is "extremely unlikely to be hazardous." In addition, containment experiments involving animal cell-transforming viruses have been substantially reduced, based on the supposed inefficiency of infection by naked DNA. Both these decisions do not take into account the results of the Rowe-Martin risk assessment experiments with polyoma virus which were reported at the Falmouth Conference. This experiment showed that naked polyoma DNA, when injected into the blood stream or tube-fed into the colon of mice, caused low-level infection.

Rather than lower the containment for recombinant work with viruses, this experiment should encourage us to maintain the original stringent containment levels for such viruses.

My office has long been concerned with the over-delegation of authority by NIH to research institutions.

The proposed revised guidelines, however, delegate substantial authority and flexibility to individual institutional biohazard committees, and lay the foundation for inconsistent protocols around the country. The IBC's are given the authority to choose between various containment combinations and to reduce containment levels at their discretion by one step for well-characterized clones. Such a system will inevitably lead to non-uniform compliance, and a subsequent disrespect for the NIH guidelines.

The IBC's are being entrusted with vast federal administrative power. Researchers and IBC's should follow uniform guidelines, not decide them. This applies equally to the inspection and oversight responsibilities given to the institutional biohazard committees. It is the duty of NIH to administer a granting program, and to ensure compliance with the guidelines. This role cannot be delegated to its grantee institutions without raising serious conflicts of interest.

We recommend that the membership of the Recombinant DNA Advisory Committee be expanded to include a greater proportion of representatives of the public interest, and individuals with knowledge in public policy. The decisions made by the Recombinant

Advisory Committee extend beyond strict technological assessments. They involve the social impact of a vast technology and therefore should have members representing all aspects of its decision-making functions.

We also recommend that the institutional biohazard committees expand their membership to include representatives of the state or equivalent local health department, as well as a member of the laboratory workers engaged in the recombinant DNA research. We recommend that a biohazards officer be appointed at each institution, not just for those engaged in P3 and P4 level work.

No NIH grant should be awarded until a specific kind of medical monitoring and record keeping is prepared. The medical monitoring plan should include periodic check-ups, and maintain accurate records on incidence of illness among all recombinant research personnel, all incidence of accidents, spills, and recombinant organism releases, and the location and conditions of recombinant DNA organism containment. These records will be particularly important if it should become necessary to establish legal liability at a future date in case of an accident or sickness.

A central clearinghouse should be established at the federal level to which copies of all medical

surveillance plans and records should be filed. Such a clearinghouse, containing records of all recombinant organisms, accident reports, and medical records, would be invaluable in ascertaining biohazard risks from recombinant research, and establishing safety records of particular laboratories and containment methods.

Detailed emergency cleanup plans should be drawn up by the biohazards officer and the institutional biohazard committee for each recombinant DNA project. Such plans should be submitted to the NIH for approval along with the grant application, and be stored in the central clearinghouse.

In the event of any release of recombinant organisms or of noncompliance with the guidelines, the state or local health authorities should be immediately notified. The effects of any accident will be first experienced within the local surroundings. Consequently, the state health department or its local equivalent should be informed at all times of what organisms are being used, and of all releases of recombinant organisms, even those considered minor.

In summary, the New York State Attorney General's Office believes that there is insufficient scientific justification for the relaxation of containment levels contained in the proposed revised guidelines. On the

contrary, the expression of eukaryotic DNA in bacteria, exhibited in such experiments as the successful insulin production work, prove that higher and lower organism gene boundaries can and will be crossed by nan. The Rowe-Martin experiment shows that naked DNA, far from being inactive, does infect cells. Unsubstantiated claims of the safety of recombinant DNA research pervade the Director's Decision Document, and the Environmental Assessment Document, and are reflected in these new proposed guidelines.

We strongly believe that the containment measures are too lax and should be increased in order to protect health and environment. By delegating increased authority to IBC's and allowing them wide discretion in setting containment levels, the proposed guidelines insure confusion and disrespect in the implementation of the guidelines. A uniform set of guidelines is a necessity for the safe conduct of recombinant DNA research.

Finally, provisions for reinforcement of the guidelines are inadequate. NIH should enforce the guidelines and monitor its grants for recombinant DNA research. Yet, the revised guidelines delegate respon-sibility for inspection and oversight to the IBC's. This, we believe is an improper abrogation by NIH of

its duty to administer its grant program. Enforcement of the guidelines cannot be left to the IBC's and the institutional beneficiaries of the grants. There is an obvious conflict of interest. Instead, NIH should allocate sufficient funds toward the administration of its grant program, providing for personnel and equipment to inspect grantees. If NIH sponsors this research with public funds, it has a duty to that public to ensure that recipients of grants comply strictly with the rules.

The New York State law requires state oversight and inspection. The federal government should do no less.

MR. LIBASSI: Thank you very much.

MS. FEINBERG: Would you like copies, or should I leave them on the desk?

MR. LIBASSI: I think we have gotten copies of your statement already. Thank you.

Norton Zinder is next. And I take it that Dr. Szybalski is not here.

DR. ZINDER: I am Norton Zinder. I am Professor of Molecular Genetics at the Rockefeller University. I also happen to be a member of the old boy network, so I am going to make a rather personal statement. Old boys are allowed to do that.

Almost five years ago, I was a member of the committee generally known as Berg et al., whose actions

led, through a rather torturous path, to this hearing today. However, I am here to celebrate the revision of the guidelines and not these hearings. I can't speak for Berg et al., but I do believe that when we discussed the power of the new recombinant DNA techniques and its potential biohazards, we turned to what we knew would be most effective -- peer review. We envisaged and then initiated a process whereby there would be continuous expert peer review of the procedures needed to perform these experiments safely. The revision we are discussing today is in part the result of such a process.

When we asked the NIH to prepare the first set of guidelines, it was not -- and I repeat -- it was not because the NIH was a granting agency with latent regulatory authority over federal grantees. It was because NIH has the primary responsibility for biomedical research in this country, and access to the expertise needed to perform the ongoing assessments. We almost asked the NSF. And I think Don Fredrickson would probably have been happy.

(Laughter.)

It was to be a voluntary system that applied to everybody, accepted by all because it was the rational way to proceed. The new provision in the PRG concerning

the registration of non-NIH grantees, including industry, is thus, in a sense, a step in this direction. We always assumed that these other groups were to be subject to the guidelines.

Two other points in the PRG are particularly noteworthy: the exemptions to the guidelines, and the new responsibilities of the IBC. The clear exemption of most free recombinant DNA from the guidelines is a considerable step forward. Not only did this facilitate manipulations needed to characterize DNA, such as electron microscopy, and enzyme cleavage analysis, but it also recognizes, finally, the fact that DNA itself is not in any way a toxic substance. Unfortunately, the idea that DNA functions only as hereditary information has been somewhat difficult to explain. In my own experience, lay audiences and reporters exhibit considerable surprise that electron microscope pictures of recombinant DNA look just like any other DNA.

The exemptions for self-cloning and E. coli-related microorganisms are also a welcome addition. There should have been such a category from Asilomar onward. Few can maintain that such experiments have any potential conjectural or other level of hazard. Cloning coli phage lambda and resecting it, or inserting coli DNA into it represents a class of the most benign experiments

but most useful type.

The principle of the containment level matching the most potentially hazardous component should apply here, just as well as in the rest of the guidelines. No danger, no containment. The absence of this null category has in the past in part clouded public discussions, because despite the series of graded containment levels, recombinant DNA researchers are always visualized as one single thing. And if hazard was assumed for any of its parts -- for example, forbidden experiments -- then the whole thing was hazardous.

I think we just heard some indications of that kind of reasoning.

The new duties of the IBC will make the guidelines a bit more like guidelines and less like rules. As the guidelines note, one can't anticipate every kind of experiment. Hence, flexibility is needed. Basic research moves in erratic directions because its data base is continually changing. New information, ideas and techniques suddenly appear, and experimental approaches are modified, dropped, and new ones initiated. A distantly approved MUA tends to codify one approach. Were the guidelines really guidelines, most amended MUA's wouldn't be needed. New approaches generally fall into the category of previously approved. Under the new system it would require only a

meeting of the local IBC to certify moving in a very logical direction.

In sum, all of those involved in the preparation of the PRG should be commended for their attention to detail. I strongly recommend that the PRG be approved as soon as possible so that the work may proceed.

Up to this point I have addressed myself to the guidelines in their given context. I would like to speak more generally about recombinant DNA research.

When Berg et al. spoke out four and a half years ago, they did so forthrightly. Other commentators have added other adjectives. One of our group, my friend and colleague Dr. James Watson, publicly apologized for his role in this event at the Advisory Committee to the Director last December. I understand and respect his feelings. My own are somewhat different.

I believe that given what we knew at the time, we did the conservative thing. However, I too have now become convinced, as have most of my scientific colleagues, that special regulation of recombinant DNA research is unnecessary, so why all the fracas?

Our major error was in not realizing how readily this issue would become politicized. Political perceptions have continuously played a significant role in the events of these past few years. The issue was used in some ways to

frighten the public. Thus, every move the scientists made to protect the public and allay its fears had the opposite effect. With the development of biological containment even more fear was engendered, since previously physical containment was adequate for the most dangerous organisms known. Special containment certainly meant special hazards.

Discussion of risk assessment experiments even led to a lawsuit in one instance. The scientists were caught in an enormous Catch 22, and put on the defensive, and somewhat bewildered, especially since there wasn't a tangible hazard in sight. Peer review broke down, and the current NIH guidelines were motivated, I believe, more by politics than by science.

The controversy itself was indeed establishing the existence of hazard. It was in fact the very hazard itself. A somewhat remarkable illustration of this point is contained in a letter from Mr. Peter Hutt of Covington & Burling to Dr. Gilbert Omenn of the OSTP. He is talking invocation of PHS-361. "With specific reference to research on recombinant DNA molecules," he says, "the question has been raised whether there is sufficient danger of communicable disease to justify invocation of Section 361. If indeed, there is no significant possibility of this occurring, it is difficult to understand why the

U.S. Congress, the NIH, the entire scientific community, numerous state legislatures and city councils and citizens group have been spending such an inordinate amount of time debating it." He concludes, "The very nature of the controversy itself is sufficient, in my judgment, to establish the potential for harm under Section 361."

This may be good politics, yes, but it is certainly not good science.

Can we return to something approaching normality? The revised guidelines are clearly a step in this direction. The question that now must be asked is what advice will the newly convened Berg et al. committee, and certainly I mean its equivalent, give us now? At the least, three points would enter their deliberations. First, that the great promise of research with recombinant DNA has been and continues to be fulfilled. Numerous scientific advances in our knowledge of basic biology have been made. Sooner than we had any right to expect, the work yielded useful products.

Second, although there have been thousands of experiments, there has not been a shred of evidence of harm to either health or environment.

Lastly, the scientific community believes now, almost unanimously, that work with recombinant DNA is at least as safe as is any other biological research. A fact

often forgotten is that in 1973 and '74 the scientific community itself was most skeptical. After a long period of intensive discussion and analysis it has satisfied its collective mind. It should be listened to.

Given these three facts, I fail to see how any committee would not recommend a dismantling of the edifice that has been constructed to regulate this research, and to do so soon. As long as the guidelines persist, the presumption of danger persists. Perhaps as the first move in this direction they could become guidelines. The procedural aspects of the guidelines could be dispensed with -- the regulations, the ORDA, the IBC's and the MUA's. This would leave the containment procedures intact for a period of time, during which expert committees would continue to re-evaluate the necessity for any special containment for any aspects of this research.

In sum, I recommend that the PRG be approved as soon as possible, followed by a hard and fresh look from the fresh perspective on the whole issue of research with recombinant DNA.

Thank you.

MR. LIBASSI: Thank you very much.

If Judy Berek is not here, Pamela Lippe is next.

I must say, as a lawyer and as a relative newcomer to this issue, I find the format very frustrating. I sense as one speaker is speaking that there is a wave of desire to answer. Then the next speaker comes up, and I feel the wave go the other way across the room.

(Laughter.)

I just sort of sit here frustrated, saying I wish we could do this in a little more informal format. It might be even more fun. But I hear all the silent comments going back and forth across the room.

(Laughter.)

Okay, Pamela Lippe, go ahead.

MS. LIPPE: My name is Pamela Lippe, and I have been lobbying for Friends of the Earth for close to two years on the federal legislation to regulate recombinant DNA. Due to the time considerations I will have to be brief with amenities, but we do appreciate the opportunity to express our concerns once more.

We in the public interest community look at recombinant DNA as a powerful new technique and technology with unprecedented potential for both benefit and harm. Contrary to recent scientific pronouncements, we do not want to stop recombinant DNA research, or scientific progress. We simply wish to achieve the benefits without

incurring unnecessary risks.

The scientific community looks at recombinant DNA as a powerful tool which will allow them to answer questions beyond their previous understanding, and to do things that stretch the limits of their imagination. Very exciting stuff.

While it is understandable that scientists more clearly perceive the beneficial aspects of their efforts, a quick survey of recent scientific and technological breakthroughs illustrates the time bomb and elusive nature of many of science's most cherished dreams. As the Stevenson subcommittee pointed out in its recent oversight report, "At issue is the extent to which research scientists should be entrusted with responsibility for their own conduct individually or through peer review, or should be subjected to external control and scrutiny."

Our position is that if the situation is serious enough to develop guidelines for the conduct of this research, then it is serious enough for the guidelines to be enforced. Self-regulation has never worked in the past; there is no reason to expect recombinant DNA to be any different.

In general, my comments will focus on the procedural aspects of the guidelines, as requested by

Secretary Califano. I hope you will find these comments and recommendations useful.

Scope and applicability. In general, we support efforts to further extend the guidelines to the private sector, such as those in the proposed revisions. It is unfortunate that no more comprehensive mechanism exists to transform the guidelines into full-fledged regulations -- legal authority extending to industry and academia alike, and to both effectively.

We would still urge that HEW use Section 361 of the Public Health Service Act. Congressional inaction on this issue does not in any way diminish the need for meaningful regulation in this rapidly developing new field. It was hardball politics, not new data, that killed the House and Senate bills.

The new data, discovered and/or developed in only one year's time, offers assurance about one small part of the potential danger, E. coli K12. We are already considering approval of new host-vector systems, deliberate release into the environment, and exempting research with wild-type E. coli. What little we know now will become even less as we continue to open broad new biological and ecological vistas.

We urge you to reconsider your decision regarding 361 in light of the inadequacy of the existing

NIH proposals, as pointed out in today's testimony, and the need for legally enforceable regulations due to increasing interest in the private sector. Even if Congress acted next session, which is highly uncertain, it would be a minimum of two years before regulation would be in place. I hope you will agree with us that the drawbacks of that course of inaction far outweigh the use of Section 361.

We would recommend, one, that you promulgate the guidelines as regulations under an existing authority. In the absence of full regulation under existing authority, could NIH-funded investigators require an approved MUA with certification on file with the NIH prior to shipment or transfer of recombinant DNA materials?

Exemptions. The requirement for the fourth class of exemptions is that they "exchange DNA by known physiological processes." There is no longer a requirement that they must be "natural" physiological processes. "Known" is a much broader class of exemption. How does the NIH define it?

More significantly, there is no requirement that that particular class of exemptions be "safe."

We would recommend that, one, all exemptions be made on the basis of proven safety based on experimental data -- i.e., no significant risk. The list of exchangers

should be by species, not genus, and added only on the basis of safety as well as exchange. Three, there should be full compliance with NEPA.

Exceptions. The guidelines point out that weight must be given to scientific and societal benefits and potential risks, acknowledging that these decisions are not only technical, but political. This situation demands much broader representation in the decision-making. Appropriate notice and comment is simply not adequate. The decision is already made. The decision-makers can and do ignore public comment.

Exceptions are easements of prohibitions. These experiments were not prohibited lightly; the ban should not be lifted without careful consideration of all possible consequences, drawing on the full range of expertise.

Recommendations. All exceptions from the guidelines should be undertaken only after a full Environmental Impact Statement to allow for assessment as well as better public input and awareness. In the case of a single risk-assessment experiment, where containment will not be breached, an EIA may be satisfactory.

Waiver on large-scale culture size should only be granted after full-scale risk-assessment studies on the organism and an EIS on the large-scale production

process have been done. The guidelines presently state that prohibition of deliberate release into the environment should be lifted only if the requirements for a waiver are met and if the requirements of NEPA are considered. What are these requirements for a waiver, and are the requirements of NEPA going to be met, not only considered?

Certification of Host-Vector Systems. New host-vector systems raise a whole new range of ecological and biological issues. The projections of safety being made from E. coli K12 are no longer germane. These decisions must be made on the basis of as complete knowledge as possible. The NEPA process will help to inform the decisions.

Responsibilities of the NIH. Due process considerations. The reference to shifting the burden of proof should be stricken from the guidelines. As discussed earlier, it is clearly premature. For an excellent discussion of where the burden of proof lies, I urge you to read Peter Hutt's March 3, 1978, letter to Dr. Fredrickson, page 2.

Appropriate notice and opportunity for public comment is an inadequate participation mechanism. By that point the important decisions have been made. Our comments in the past have too often been ignored. The public perspective must be introduced at a much earlier point

in the decision-making.

In that regard, the Director's Advisory Committee does not adequately substitute for public involvement on the Recombinant DNA Advisory Committee. Once again, decisions are made by the time the public gets input. It is this kind of public participation that has led to distrust of the policies of the NIH.

Public membership must be substantially increased on the RAC. As the Stevenson subcommittee concluded, "The technical and social policy aspects of even physical and biological containment standards, or host-vector approval, cannot be readily distinguished." Scientific decisions cannot and should not be separated from their social and political context. In attempting to do so, the NIH has insured the decisions were made simply in a less representative social and political context.

The Recombinant DNA Advisory Committee. The RAC has turned out to be much less conservative than the Director of NIH. In many cases they went further in the PRG-RAC than the Director finally allowed in the PRG-NIH. Advisory committees have been often expected to counter-balance internal conflicts of interest, and in this case insure the public health and safety is being adequately considered. Unfortunately, the RAC does not seem to be

fulfilling that function.

Recommendations. EPA, OSHA, FDA and CEQ should have full voting membership on the RAC. This is essential now that the NIH is accepting voluntary compliance by industry. In order to protect proprietary information, the RAC will have to hold meetings not open to the public. We need to have some assurance that our concerns will be represented.

Perhaps more importantly, the RAC could use the advice of experienced regulators, particularly as they begin to deal with industry.

The Interagency Committee is not adequate participation and input for these agencies. It has not met once this year. The advice of EPA and OSHA in particular will always be appropriate, as referred to on page 33051, they should be fully involved in the decision-making.

The majority of open spaces on the RAC should be filled with individuals nominated directly by the public. Until we have members who share our perspective, and whose judgment we trust, the decisions of the RAC will always be suspect. This trust is in the long-term interest of the NIH as well as ourselves.

Penalties. HEW must find some mechanism by which penalties can be assessed appropriate to the infraction, and then use them as required.

Responsibilities of the Institution. Health Monitoring. Institutions are only required to determine the necessity of doing health monitoring, not to actually do it. There is nothing in the guidelines that requires medical monitoring, data collection, maintenance of records, or, for that matter, good experiments designed to determine if anything is happening with recombinant DNA organisms inside human bodies.

Very little study has been done on the epidemiology of recombinants in humans, and although we have heard repeatedly that no one has been injured in this kind of research, they are still saying that about commercial nuclear reactors.

It is important to note that the most dangerous kinds of experiments have not been done. Almost all the work has been executed with safer recombinants.

Recommendations. Make mandatory requirements for data collection and record keeping in a unified manner, obviously allowing for easier accumulation and analysis.

Carry out an assessment in a year or two to see if the centralized collection of this data is required.

Institutional Biohazard Committees. The NIH has delegated considerable authority to the IBC's to allow research to proceed prior to NIH approval on changes in P1 through P3 protocols. This policy will lead to confusion

and discrepancies between institutions. Approximately ten to fifteen percent of all MUA's are disapproved by the NIH on non-trivial grounds. This creates ample opportunity for problems.

Recommendation. Require prior NIH approval on non-trivial changes on P2 through P4. If significant delays develop, hire more staff, fund less research -- one staff person worth.

The IBC's approve single-step reductions in containment levels for experiments with purified DNA and characterized clones. Authority for single-step reductions in containment levels, as well as the previous provision, will lead to a patchwork of regulations, which was decried by the scientific community in regards to federal preemption of stricter standards but is apparently welcomed for lowering them. Furthermore, there is no requirement that these fully characterized clones or purified DNA be safer.

MR. LIBASSI: Do we have your full statement?

MS. LIPPE: Yes, you do.

MR. LIBASSI: All right, thank you very much. We will get the rest of it there.

Jonathan King? Why don't you go ahead now.

DR. KING: Good morning. Thank you for this opportunity to testify. My name is Jonathan King. I am

Associate Professor of Biology at MIT and Director of the Biology Electron Microscope Facility. I have published papers in the area of microbial ecology, and in particular, survival of the micro-organisms in extreme environments such as Antarctica, as well as many papers on the structure and assembly of the viruses that are used as vectors in recombinant DNA research, and on hazards of recombinant DNA research themselves. However, I have never served on an NIH committee in this area. I testify here as a member of the Steering Committee of the Coalition for Responsible Genetic Research.

Reaping the potential benefits of recombinant DNA technology clearly requires containment of the potential hazards. I find no substantial evidence or argument presented in the draft revised guidelines or supporting documents to justify the major weakening of containment proposed therein, such as reduction of containment for shotgun experiments with DNA from birds and mammals, and the lowering of containment for cloning of eukaryotic viral DNA's.

The draft guidelines and supporting documents that are representing considerable labor and effort -- in many ways a very careful document -- are marred by four major failings. One, the absence of the most relevant

observations which form the basis of the need for containment in the first place, and which should always be at the beginning of any standards document. Two, a major logical fallacy which pervades the entire set of documents, in which the ability to safely perform a process or handle an organism is confused with the intrinsic hazard of the organism or process itself. Thus, one can safely handle iodine 125. This does not mean that iodine 125 is safe. In fact, to develop safe handling, you have to understand what will happen if you don't safely handle it.

Three, a heavy reliance on unreferreed, unexamined reports of small committees meeting in private, which are then presented as the consensus of the international scientific community, such as the Ascot report. My own concern in talking about participation is in the public of scientists, much broader participation of other NIH-sponsored scientists.

Four, extraordinary "selectivity" in the documents in which no arguments which counter or fail to support the proposed changes are either quoted or referred to.

To expand on these points, some key observations whose absence from the documents erodes my confidence in the RAC: A, in the United States Escherichia coli strains are the number one cause of community-acquired infections serious enough to cause hospitalization (Gangerosa, 1978, Journal of

Infectious Disease). B, E. coli strains are the number one cause of hospital-acquired infections in the United States. These infections are not gastroenteritis; they are acute infections, generally uterine, surgical wounds, pneumonia infections in the respiratory tract, and bloodstream infections -- bacteremias.

To give you a sense of this, a recent survey of gram-negative hospital-acquired infections by Stan, Martin and Bennett, Journal of Infectious Disease, August 1977, indicates as follows: Each year in the United States at present, there are 90,000 surgical wound infections due to E. coli strains, with 2,700 associated deaths. There are 40,000 nosocomial pneumonia infections due to E. coli strains, with 10,000 associated deaths. There are 17,000 bloodstream infections by E. coli strains, with 4,000 associated deaths. All these patients are compromised, they are in the hospital, they have been operated on, they are weak with something else, they are getting immunosuppression, and that is why they are getting sick. But of course, in general, that is who gets sick from infection -- compromised patients.

I should add here that my own concern has always been, right from the beginning, not the conversion of K12 through a pathogen, but the transfer of a vast variety of genetic information into strains which are indigenous in

the population, or are already epidemic.

C, epidemic strains of E. coli are well known, causing, for example, diarrhea in adults and in infants. They have been a particular problem among infants. To quote Dr. Bradley Sack in a recent editorial in the New England Journal of Medicine: "Benign-appearing, but enterotoxin-producing Escherichia coli have been recognized as important worldwide etiologic agents in diarrheal illness of children and adults."

D, in numerous well-studied cases, the pathogenicity of E. coli strains for a particular host is associated with plasmid genes -- that is, the plasmids that are the hosts in the recombinant technology for the foreign DNA: antibiotic resistance, enterotoxin production, production of proteins that allow the coli to colonize a site that they normally wouldn't -- for example, the K88 antigen associated with disease in piglets.

The failure of the guidelines to point out the clear analogy between the known pathogenicity associated with proteins coded for by plasmids, which interact with the mammalian cell and therefore cause pathogenesis, and the introduction through recombinant DNA technology of a gene into a plasmid, coding for a protein that, since it comes from a mammal, is very

likely to interact with mammalian cells, is incomprehensible to me on a scientific basis.

E, pathogenicity is not a property of an organism, it is a relationship between the organism and some host. For example, a particularly serious form of E. coli infection is infantile meningitis. This is described recently in an article by Gload, et al., in the Journal of Infectious Disease. It is reviewed in the current issue of the Annual Review of Medicine by Katherine Wilford.

Infantile meningitis has a very serious mortality rate. It is at 40 to 80 percent, and many of the infants -- these often premature infants, neonates, who survive the infection -- are developmentally and neurologically impaired. The strains that cause meningitis in premature infants are not pathogenic in adults, in their mothers. Therefore, if you test these strains which show a particular antigen, K-1 antigen in a healthy female, you don't get meningitis. She doesn't get sick. That is not the proper host.

All of the discussions of the Falmouth Conference, at which I was present (but again, not invited), focused on the pathogenicity of E. coli in healthy adults and not in compromised individuals, which brings me to the general point missing, F,

that there are many possible subsets of susceptible individuals in the population. These people are normal targets of infection. They include individuals receiving immunosuppressive drugs as therapy, obviously newborn infants, premature infants, the elderly, et cetera.

The guidelines make no mention of the problem of autoimmune disease, which I explicitly laid out and published in the proceedings of the Falmouth Conference. These are the baselines on which one might be concerned about the transfer, for example, of a gene coding for a human growth hormone, somatostatin, or insulin into an indigenous strain of E. coli, and why it is important to contain these bugs.

Now, two, in the absence of a scientific discussion of why one must contain the introduction of foreign genes introduced into K12, what we have is a continuous repetition of a logically fallacious and scientifically irresponsible argument. To wit, if we follow the guidelines and clone in weakened strains, there is very little hazard. Therefore, there is very little hazard to recombinant DNA research in general. Therefore, we can weaken the guidelines, and not require debilitated organisms. Then this argument is repeated again and again, since in the somewhat less debilitated organism, EK1 and EK2, there doesn't seem to be evidence for escape -- that is, there is containment. Therefore, there is no hazard; therefore,

the whole concern about the hazards of recombinant DNA is out of order.

I submit that anybody who had any experience in the setting of industrial standards, such as asbestos or vinyl chloride or anything like that, reading these guidelines, would immediately recognize the absence of the separation of the intrinsic hazard and the ability to contain it.

Therefore, I very much support the expanding of the technical basis of the RAC in this area.

Now, three, I would like to go to this question of--You know, if you read the regulatory literature--for example, in asbestos--it is an old thing in which a committee appoints some independent, outside committee who -- okay -- quickly, the Ascot Committee.

Twenty-nine individuals appointed by the NIH through a process I don't know -- very respected virologists, many of them colleagues of mine. They met in private in England. They didn't even notify the British committee, GMAG; the report was not published; it wasn't published in the Journal of Virology, it wasn't published in Virology, it wasn't referreed--Recently I was at the International Congress of Virology, where I chaired a workshop on virus assembly. There were 1,500 virologists there. This report--

neither the questions were raised in any workshop, the conclusions were not brought forward in any workshop. Even in the plenary session no member of the committee got up to announce that this report existed, which offers itself as the consensus of the wisdom of virologists. Yet we have here the guidelines substituting a report from 29 notable individuals -- and I agree with many of their conclusions -- substituting this for the consensus of the international virologic community, who doesn't even know that these decisions were made.

Now, what is in that report, much of it is correct. It is notable for what is lacking from it.

Thank you very much. I have a more detailed statement, which will be submitted.

MR. LIBASSI: Thank you.

Sheldon Krimsky? Thomas Blessing?

MR. BLESSING: My name is Thomas Blessing. I presently serve as the Drain Commissioner for Washtenaw County, Michigan. The position is a county-wide elected position, serving a population of 260,000. Prior to involvement in the public policy questions of my present position, I gained detailed experience in air handling equipment as Head of Research and Planning for the City of St. Paul's Air Pollution Control Agency. If one couples this experience with my work as a research

assistant in a laboratory studying photosynthetic bacteria, I believe I can offer a unique perspective to the public policy questions that arise from recombinant DNA research. There are many others who will go into depth and have gone into depth on the specific technical aspects of it.

I would like to state at the outset that to me, quite clearly, the decision-making on this issue has been dominated by a scientific community that is enamored with visions of new discoveries and exciting breakthroughs. I am not surprised. Many of these visions may well be fulfilled. Recombinant DNA research technology is a very powerful biological tool. And the NIH, I believe, has responded to this enthusiasm, but has not responded to statements calling for caution.

Statements throughout the introduction refer to, and I quote, "overwhelming sentiment," page 33043; "growing sentiment," page 33044; and "general endorsement," page 33051. This seems to be used as the justification for initiating the relaxation of standards. The fact that this "sentiment" and "endorsement" consists almost exclusively of those with a vested interest in rapid, unfettered research has conveniently been set aside.

The policy questions and the social risks of a tool as powerful as recombinant DNA research are simply being ignored by the present decision-makers. The result is a set of guidelines that does not reflect the kinds of concerns that such decisions properly require. For example, page 33043 of the guidelines has the statement, "there was overwhelming sentiment for exempting from the guidelines experiments involving recombination of DNA within the same strains or from pairs of organisms that transfer genes in nature." Page 33051 addresses the question of the public's role in the exemption process by stating, in part, "the membership of the RAC will be broadened modestly, as needed for expertise, but provisions for public notice and opportunity for comment can be used to ensure adequate public input when the issues warrant."

I ask, who will decide when the issues warrant that, and how can a modest increase in the RAC serve to provide the broad perspective that is necessary for the social concerns that are involved with recombinant DNA research?

The revised guidelines begin to implement this philosophy under language found in Part I-E-4 and E-5, and Part IV-B-1-d. The underpinning for these roles must be the assumption that if it occurs in nature it is okay.

This totally ignores the question of the rate of recombination under forced laboratory conditions. The parallel and equally fallacious argument is because nuclear fission occurs naturally on earth, regulation of experimentation can be minimal and exempted by an appointed Washington official.

Whoever at NIH is accepting the proposed exemption criteria is adopting a simplistic notion of reality.

In general, NIH is seeking to relax the safeguards imposed on various experiments. Physical containment is simply not the failsafe system you are being led to believe. While in St. Paul I personally inspected the air-handling equipment of more firms and manufacturers than most people will see in a lifetime. While taking courses in environmental microbiology, I studied and performed the sampling for microorganisms in hospitals and their clean rooms--what they called their clean rooms--for burn patients and the like. And all of these systems would fail on occasion. No exceptions.

We have technologists who at the present time self-regulate, and I believe their track record is poor. The most recent example, Science News reports in the September 9, 1978, issue that a new case of smallpox has been contracted by a photographer in the Birmingham

University Hospital Medical School in England. The virus was being stored one floor above his work area. I don't know what safeguards were being taken; however, I am sure that the laboratory involved presumed them adequate. This is one example.

Now NIH is proposing to relax safeguards and limit the decision-making of exemptions to a group that lacks a general public policy perspective. This is simply not acceptable.

What I have wanted to do, and make sure I got directly to you for the record, was just to touch on some of the problems within the guidelines. I have spoken of the problems with the exemptions, and of the basic decision-making structure of the guidelines. What I would like to ask you specifically to do is to redraft the guidelines to reflect these concerns.

Now, adopting the "good old boy" privilege, I would like to continue a bit more on some informal comments, addressing the question of biological containment, which is proposed to substitute when physical containment fails.

The probability of a person having a pure culture, it is chance to end up with a pure culture in biological research. It is not something that occurs naturally, and it is something that a scientist will strive to attain. It is my belief that if someone is performing an experiment

with 10 liters of sample, they simply have to be kidding themselves to believe that there is zero contamination, that there is zero organisms other than the one that they believe is in the sample.

With the kind of tool that recombinant DNA technology is, it is being performed presumably on the less viable organisms that predominate the sample, but it would also be performed on the organisms that one never knows are in there. That is what is of great concern to me and I believe to a number of people. Biological containment is not the final answer either.

I would like to conclude my remarks by saying I am not personally opposed to the research. I think that there is a place for it, that a great deal of good can come from it. But it is not something that can proceed without very careful guidelines. It is not something that can proceed with guidelines and decision-making being performed solely by the people who are directly involved with it. They simply do not have the general public policy perspective. That interface of technology and public policy must be maintained. We need to have the interface. It can't only be the technologists in this instance governing themselves.

Thank you.

MR. LIBASSI: Thank you very much.

Christine Oliver is the next speaker.

DR. OLIVER: My name is Christine Oliver. I am a physician, board-certified in internal medicine, and a Clinical Associate in the Department of Medicine at the Massachusetts General Hospital in Boston, Massachusetts. I also have a Master of Public Health degree in occupational health from the Harvard School of Public Health. I am currently working with the Oil, Chemical and Atomic Workers International Union. I am speaking today as a representative of the union and for the union.

I will address today the issue of recombinant DNA research as a threat to the collective and individual health of the potentially exposed worker, and the proposed revised NIH guidelines as they relate to that threat. I will attempt to put the issue into perspective by discussing briefly the health and safety situation as it currently exists in many other work environments.

During the past eight weeks I visited five industrial plants whose workers are members of the OCAW to assess the health hazards in these plants. These plants include chemical plants in New Jersey and Louisiana, oil refineries in Louisiana, a pesticide plant in Tennessee, and a chemical pesticide plant in Illinois. Each employs at least 150 production workers. Each is subject to OSHA regulations, and in each plant the workers are represented

by a strong, health-oriented union.

What I found in each plant was an abysmal failure to abide by OSHA regulations, and the dictates of human conscience to provide for the worker a safe and healthful workplace. The following are examples:

One. With two exceptions, each company refused to furnish the workers with a list of the generic names of all the chemicals to which they are exposed, and in the cases of the exceptions, no data on chronic toxicity, such as cancer of the lung, cancer of the liver, and delayed neurotoxicity were supplied.

Two. There was at best sporadic environmental and biological monitoring for exposure to known carcinogens, and respiratory and nervous system toxins, and there was a failure to inform workers of the results of the monitoring.

Three. There was no ongoing collection and analysis of relevant morbidity and mortality data.

Four. There was inadequate to nonexistent labeling of vessels and pipes containing toxic and carcinogenic substances.

Five. Local and general exhaust systems were poorly functioning, and for the most part, in fact, were nonexistent.

Finally, many of the workers were experiencing adverse health effects as a result of these hazardous

exposures. In one chemical plant, for example, 90 of 125 workers had abnormal liver function tests.

These situations exist despite the fact that worker exposures are to chemicals whose effects are at least reasonably predictable, and in some cases, reversible; despite the fact that both environmental and relevant biological monitoring techniques are available; despite the fact that OSHA regulations are applicable; and despite the fact that the workers are represented by a strong union.

In contrast is the situation that exists with regard to worker exposure to recombinant DNA material. One, the nature and reversibility of the effects of worker exposure to recombinant DNA molecules are unknown and in many cases unpredictable. And in fact, the effects of exposure to the attenuated organisms containing the recombinant DNA material are unknown. For example, a prospective study of the ability of the "benign" E. coli K12 to colonize the urinary tract of exposed laboratory workers has not yet been done. And yet, E. coli is responsible for 70 to 80 percent of urinary tract infections in this country, and such infections afflict five percent of the general medical clinical population. Urinary tract infections are a major source of bacteremias in this country, and kill from 66,000 to 165,000 people

per year.

Two, since the effects are not known, accurate biological monitoring for the effects of the exposure to recombinant DNA material is impossible. Latency periods are unknown and unpredictable. Thus, the establishment of cause and effect, and ultimate prevention of permanent adverse health effects are impossible.

Three, adequate techniques for environmental monitoring for recombinant DNA molecules do not exist, so that with neither accurate biological monitoring nor adequate environmental monitoring, the ascertainment of the level of worker exposure to recombinant DNA material is impossible, and thus an assessment of the risk is impossible.

Four, contrary to the statement in the July 28th Federal Register, page 33065, that "OSHA standards and procedures apply to most institutions," OHSA regulations do not apply to university and federal research laboratories, where much of the recombinant DNA research is being done. Thus, many of the workers who face hazardous and unpredictable exposures to recombinant DNA molecules are not protected by OSHA, and they are not protected under the proposed revised NIH guidelines.

One, the "guidelines" are simply that, guidelines. They do not have the force of law behind

them, they provide for sanctions that are inadequate to ensure compliance. To wit, page 33087, "noncompliance may result in suspension, limitation, or termination of financial assistance for such projects."

Two, the guidelines do not apply to industry. To compound this error of omission is a notorious problem in industrial research of large-scale production, and as commercial use increases, production will increase, job speed-up will increase, accidents will increase, and hazardous exposures will increase.

Three, the guidelines are inadequate in their specification for biological monitoring or medical surveillance, page 33084. The institution would be given responsibility for the determination, "in connection with each project, the necessity for medical surveillance of recombinant DNA research personnel." Thus, A, the institution may determine that medical surveillance is unnecessary; B, the stipulation is for research personnel only. It ignores maintenance and janitorial staff, and it ignores the families of the exposed workers, who in many cases may also suffer the effects of exposure. C, the requirements are too nonspecific and leave too much to the discretion of the individual institution.

Four, the guidelines are inadequate in their requirement for worker education regarding the hazards of

recombinant DNA molecules. They state, simply, A, page 33053, that the NIH has a contract to develop, "minimum standards for training participants in recombinant DNA research," and B, page 33085, that the principal investigator shall, "make available to the laboratory staff copies of the approved protocols that describe the potential biohazards and the precautions to be taken."

Both provisions ignore other than research personnel who are exposed, and in my experience, industrial training programs and the provision of material safety data sheets is that they are inadequate and incomplete.

Five, the guidelines place primary responsibility, page 33085, for key technical and procedural decisions, in the hands of the institutional biosafety committee. These include the approval of recombinant DNA research projects, the approval of reduction in containment levels, the monitoring of compliance with the guidelines, and the review of approval of emergency plans covering accidental spills. This situation is analogous to the allocation to the states of responsibility for monitoring and enforcing industrial compliance with OSHA regulations. Such a scheme has proved to be disastrous for labor because of local conflicts of interest and incompetence.

Given the unknown nature of the effects of exposure to recombinant DNA material and the inability to provide a mechanism for adequate protection of the worker, the risk of recombinant DNA research would seem to outweigh the benefits.

In summary, then, the adverse health effects of exposure to recombinant DNA material are unknown and in some cases where predictable, irreversible. To adequately protect the worker from exposure to recombinant DNA material is impossible. The guidelines have limited applicability; they are nonspecific in such important areas as medical surveillance and emergency spills; and they lack adequate sanctions. Accidents are inevitable, and in fact have already occurred.

There are other, less hazardous means of achieving the same ends. To promulgate such a set of guidelines that is neither enforceable nor adequate, nor applicable to all recombinant DNA research, is an unconscionable act that will create a false and dangerous sense of security.

Therefore, the Oil, Chemical and Atomic Workers International Union, in order to protect the present and future health of this country -- both the worker health and the public health -- has no choice but to maintain what has

been its position all along, and that is to call for a moratorium on all recombinant DNA research.

MR. LIBASSI: Thank you very much.

What I would like to suggest is that we hear the next three witnesses, Carl Kline, Daniel Liberman and Grace Ungers, and I would like to propose that we then break for lunch, at about 12:00, to reconvene at 1:00. And at 1:00 we will hear Daniel Nathans and Carl Anderson. We will start with those two at 1:00. There is a cafeteria upstairs on the 8th floor, which has hot meals, sandwiches, salads, hamburgers. We have a fine cafeteria here. This is a paid commercial.

(Laughter.)

Those who want to can, of course, go across to the North Building, and in the basement there is another cafeteria, but we will try to reconvene at 1:00 promptly, for Daniel Nathans and Carl Anderson.

Why don't we begin now with Mr. Kline? We have three more before we break.

Go ahead.

MR. KLINE: My name is Carl Kline. I am here representing Western Maryland Clergy and Laity Concerned. Clergy and Laity Concerned is a national religious organization concerned about issues of peace and social justice. The Western Maryland chapter is located in Frederick, Maryland.

Frederick's renown began with the lyrics of Francis Scott Key, and the courage of Barbara Fritchie. It took a more infamous turn as the biological warfare center of the country, and now waits with hope and dread the new National Center for Recombinant DNA Research. Decisions made as a result of this hearing may well affect Frederick more seriously than any other locality. That brings me to the first reason for this testimony as a citizen of the Frederick area.

The nature of this hearing and the decision-making process of the National Institutes of Health betray an incredibly serious bias against the democratic process. It has been clear since Frederick was announced as the future location of the new facility that the decision had been made by a federal governmental scientific elite, that any community concern or questioning would eventually be met by patience, payrolls, and good PR. It has been one more example of government pursuing its own self-interest to the exclusion of the larger public it was designed to serve.

I am here to suggest today that the prior question still remains: Should recombinant DNA research be conducted in Frederick, Maryland, at all? Through what process has the public there given its authorization or

pledge of support.

The National Institutes of Health has a responsibility, especially in matters of complexity and controversy, to be an educative organ, to encourage debate, to support the airing of diverse opinions, to initiate public discussion and resolution, to help raise with the average citizen the far-reaching value questions involved. Cumbersome? Perhaps. But if governmental agencies will not assume some such responsibility, we should not be surprised at democracy on its deathbed.

Should the NIH guidelines be modified? When and in what manner will the citizens of Frederick be asked that question? My assumption, based on past history, is that this is their only chance. In my mind, that is socially irresponsible.

The second reason for this testimony is more specifically related to the broader issue of the hearing, whether safety concerns can be modified and revised guidelines adopted.

National Clergy and Laity Concerned has been focusing on concerns of human security. Most of that concern has been with the nuclear arms race and the threat posed by an increasingly radioactive environment. Our chapter in Western Maryland has added to that concern

the biological revolution and the dangers posed to humankind by genetic research.

We have concluded that the technical discussions about facility classification and all the steps taken to insure containment are of great immediate importance, and the present guidelines should be continued, but that ultimately those discussions, those kinds of facilities and guidelines are simply irrelevant. They are probably most helpful in relieving the conscience of technicians, but most unlikely over time to prevent serious threats to human security. Already, recombinant products, threats to human security included, are becoming the responsibility of other government agencies like FDA and EPA, with less than spotless records, and those who do the research move farther and farther from accepting responsibility for their products.

Now, perhaps we would have a more optimistic view of the future if our roots were elsewhere, or our immediate experience was different. But as members of Clergy and Laity Concerned, we are rooted in a fate that proclaims a creator, a God of all life and being, and our human security lies there; not with a laboratory technician or efficient administrative officers, or comprehensive offices of security and safety. And that you not misunderstand me, we also have greater faith in the process of

evolution and the pace at which life evolves than we have in a scientist's genetic intervention or in an NIH timeline.

Also, our immediate experience suggests to us that our faith is not blind faith. There are serious reasons why we choose to place our confidence elsewhere. There is history shaping our concerns. We received significant promises with the arrival of the nuclear age; benefits seemed to outweigh costs. Now we are forced to coin new words, like John Somerville's "omnicide," killer of all, for the nuclear reality that we face daily. And we received significant promises with the arrival of the chemical revolution; benefits seemed to outweigh dangers. Now we are forced to coin words like "ecocide," killer of the ecosystem, for the carcinogenic pollution that ravages the planet.

Again, now, we are assured of important benefits with minimal dangers, by the biological revolutionaries. And we will most likely be forced to consider genecide, spelled in a new way, with an "e" and not an "o."

Assuredly, natural recombination occurs without our intervention. Assuredly, natural recombination is a moving force in the evolutionary process -- in my understanding, in about one percent of the cases. Where violent intervention in genetic heritage occurs in the natural

process, 99 percent of the time it is harmful or detrimental to the organism involved. We contend that the most dangerous research begins when we are most convinced that we can secure our own genetic future; when we are convinced, beyond a shadow of a doubt, that we really know what we are doing; when we begin to exhibit the age-old attitude of arrogance. So the subject of this hearing convinces us that the biological-technological imperative moves us quickly toward genecide.

Now, if nothing else, this testimony is presented in the hope that as people focus on issues of human security, a minimal degree of humility will be present; that acts of God might be recognized as something other than acts of man, blamed on God; and that if we are honest with ourselves and with others, we must eventually confess that we always end up knowing less than when we started.

Finally, the directions and dimensions of the biological revolution developing from this new technology, a technology that will most likely become commonplace soon, are leading some of us in the Christian community to oppose it totally. We are being blinded to any distinctions in kinds of research by what seem to us to be misinformed and mistaken assumptions underlying the work, and by the

enormous potential for death and destruction, especially biological warfare, implicit in the work.

We are convinced that ultimate value lies in life itself. All of it is good, not simply life that is human; and we are not advancing if we increase the quality of human life and further threaten life itself. Deeper perhaps than that, as we move closer to genetic engineering, we are convinced there is something irreparably human about human genetic mistakes. Already, if diabetics have reason for hope, dwarfs beware.

In closing, I agree with Gordon Cosby that it isn't our MAD -- mutual assured destruction -- nuclear policy that has kept humankind from nuclear annihilation. Ultimately, we are still here by the grace of a compassionate God and the work of some serious peacemakers.

As we enter the genetic age, one could hope that decision-makers would worry about human security from the effects of individual and corporate greed, individual and corporate ignorance, individual and corporate power, and individual and corporate pride; as they worry about bricks and mortar, air vents and air flows, biological and physical containment. And that barring omnicide, my children would not be faced with genecide.

MR. LIBASSI: Thank you.

The next speaker is Mr. Daniel Liberman.

MR. LIBERMAN: Members of the Committee, I am pleased to have this opportunity to appear here today and participate in this hearing. I shall try to confine my comments to three areas, and I shall try to keep my comments brief.

My first comments concern the certification of HV2 and HV3 systems. The criteria for certification, and I am referring to Section II-D on page 33075 of the Federal Register, that are described, cannot be practically applied to nonbacterial systems. Specific criteria, I believe, should be developed which relate to tissue culture and other eukaryotic host systems. I will use Saccharomyces cerevisiae, brewers yeast, as an example.

Both the National Science Foundation and the American Cancer Society have approved recombinant DNA projects with Saccharomyces cerevisiae as a host, and as far as I am aware, NIH has not. I believe that specific criteria must be developed in conjunction with other grant agencies to avoid problems where various agencies can move independently in reviewing recombinant projects.

My next comments concern the definition of recombinant DNA itself, and what I would really like to do is ask questions of the Panel here, as well as the audience, to think about, because I don't know the answer.

I would like to ask the distinguished

scientists in the audience if it is possible, or even conceivable, to use RNA and not DNA vectors in cloning. Would the use of feline leukemia virus or Rous sarcoma virus as a vector to carry RNA sequences into a cell be possible under the NIH guidelines, or would it be exempted from it? And, once inside the cell, would this RNA serve, possibly, as a template for the production of a complementary DNA sequence that might be incorporated into the chromosome of that host?

I am not pointing this out to be critical of the guidelines; I just do not know the answer to this. In the original version there was an oversight, and synthetic DNA was not considered under the guidelines, and there was a good deal of controversy which followed. I think perhaps that the letters DNA should be eliminated from the definition, and "nucleic acid" should be substituted, because RNA for some organisms, is the genomic material.

The third comment I would like to make concerns the description and the role of the biological safety officer. I perhaps am fairly unique in the United States, because I am a non-federal agency, non-industrial biological safety officer who runs a biological safety program that fulfills most of the requirements described in the new laboratory safety

monograph. Now I, fortunately, have a superb technical staff and administrative staff that allow me to pursue this. The job description for the new professional in the academic and industrial community as a result of recombinant DNA research, as described in the laboratory monograph, is very difficult to be performed by a single individual. The panel that drew up this proposal recognized this, and felt that perhaps the responsibilities could be spread through an entire safety organization.

I would plead with the individuals who originally proposed that document, in that the last thing we need in academics right now is an administrative safety officer. But I think that my comments should be directed to the fact that, of the ten individuals who prepared that document, and it is an important document in biological safety -- please don't get me wrong -- six were from the NIH, two were from Frederick Cancer Research Center, one from the Center for Disease Control, and one from the National Animal Disease Center. These individuals were all experts in biological safety. However, there is no input from the academic or the industrial communities into the construction of a document which will somehow be used to regulate them in certain capacities.

I would like to point out that while they were

cognizant that the description was such, they did indicate that there were certain critical duties that this individual could perform. I would like to see these critical duties emphasized in subsequent versions of the laboratory safety monograph.

I want to congratulate that particular panel on their sincerity in preparing that document, because there are very few pieces of information that biological safety people can use. Many of us do not have the extensive experience that has been built up through the various research programs that the government has been involved in through the years.

On that note, I would close. Thank you.

MR. LIBASSI: Thank you, Mr. Liberman.

Next is Grace Ungers.

MS. UNGERS: I am speaking on behalf of both Dr. Rosenberg and myself.

Gentlemen, the use of recombinant DNA can potentially alter man and his environment for better or worse, by intention or accidentally. Therein lies both the promise and the danger of this new technology.

The NIH Recombinant DNA Advisory Committee and the guidelines were set up to minimize the hazards that might arise accidentally from various small-scale experimental procedures, mainly those of academic research.

It was academic research that gave birth to recombinant DNA techniques, and the academic research community, primarily under the aegis of NIH, has been the first to exploit the techniques as well as to recognize their possible risks. But recent syntheses of both the growth hormone and insulin, and the rapid emergence of industrial interest, show that academic research will not have the field to itself much longer. New problems are about to arise, resulting from the near impossibility of preventing the unwitting release into the environment of recombinant organisms when they are produced on a large scale for drug manufacture.

There are also problems of predicting all the environmental consequences that may result from the intentional release of large quantities of genetically engineered organisms, such as oil-eating bacteria and nitrogen-fixing plants.

But the regulation of industrial application is outside the scope of NIH, and the evaluation of the public stakes in the application of this new technology is beyond the competence of research biologists, who make up most of the membership of the advisory committees. Societal priorities, ethical questions and non-scientific judgments are going to be involved, and if the authority is not broadened and the decisions are not very

soon delegated to a more qualified and representative body, they are going to be made de facto by commercial interests alone.

Experience shows that commercial decisions have a way of becoming economic necessities that are independent of their intrinsic value. Witness the difficulties of phasing out the manufacture and use of carcinogenic insecticides like Mirex and Chlordane, and nitrite in bacon.

Nonetheless, once an unforeseen hazard is identified in these technologies, they can, in principle, be halted. Not so with recombinant DNA technology. Once a dangerous recombinant escapes and finds an ecological niche, it is likely to be impossible to eradicate. We therefore recommend not just basic research, but that industrial and other applications involving recombinant DNA should be universally regulated by the force of law in the public interest.

Turning to the proposed revisions of the NIH guidelines, we would like to point out that not only are some of them potentially dangerous and unwarranted, but they have been arrived at by unscientific methods that would never be judged acceptable for the establishment of even the most insignificant scientific fact. They are therefore all the more unsuitable for the establishment

of scientific procedures where the public safety is concerned.

After illustrating the unscientific basis for some of the revisions, we will turn to the question of how to rectify the problem.

Firstly, a great deal of weight is placed on semi-authorized reports of discussions held at closed scientific meetings attended by a small number of selected participants. The outcome of these meetings in general appears to represent the best guesses of those present, most of whom were interested parties. The proceedings of the meetings were not published for inspection and criticism of the entire scientific community before they were accepted as a basis for lowering the safety precautions.

In normal scientific practice, meetings and discussions of this kind are considered appropriate, not only as a basis for choosing more promising concepts for future experimental investigation. However, the Falmouth Conference of last year was used as the basis for down-grading the containment requirements for cloning foreign DNA in E. coli. This revision has been proposed without waiting for the results of the experiments now in progress, which were designed, under contract by NIH, to test the assumption on which the revision was based, namely that

EK1 and EK2 strains of E. coli cannot escape from the laboratory by usual routes. Recently, unexpected results have shown that the EK2 strain can survive spillage much better than had been anticipated. This indicates that caution is still in order, at least until the full results of the study become available in a year or so.

It seems to us appropriate that the scientific data on this safety question be evaluated before rather than after giving hundreds of laboratories around the country the go-ahead to lower their precautions.

Another closed meeting, held at Ascot this year, served as an ostensible basis for the drastic downgrading of containment requirements for recombinants involving animal virus DNA, including tumor viruses. Actually, the conference reportedly recommended P2 containment, but an American subgroup subsequently met and opted for P1 and EK1. Let no one suppose that P1 actually represents containment. P1 and even P2 levels of precaution may prevent massive accidents, but they simply cannot prevent ultimate escape from the laboratory.

An experiment bearing on the safety of an escaped viral recombinant DNA has already been carried out, the Rowe-Martin risk-assessment experiment with polyoma DNA. The results have never been published, but they were reported to show that a recombinant plasmid carrying viral

DNA can be infectious in mammals. Thus, the insertion of such recombinant plasmids into E. coli gives the virus an entirely new route of attack, which could be dangerous even if the coli itself did not survive after entering the animal or man. The new route might even prove to be more efficacious than the normal mode of infection by the virus.

It is therefore not correct to assume that recombinants containing virus must be less dangerous than the virus itself. Experimentation on the extent of the hazard posed by creating a new vector for cancer virus is surely called for before this type of work is permitted at all, much less under the almost totally permissive conditions proposed.

A similar argument applies in the case of bacterial types which are proposed to be exempted from the guidelines. Among those are some species which are plant pathogens, and some which have never proven to exchange genetic material naturally with certain other organisms on the list.

The Recombinant DNA Advisory Committee has recently decided that data on genetic exchange to be used as the basis for exempting organisms from the guidelines need not even be published in refereed scientific journals. Thus, the data need never be

subjected to examination or criticisms by others, with perhaps a greater knowledge of the study. Conflicting data need never come to light. A very fundamental scientific control involving peer review has been sidestepped. This goes to the very heart of the ethic of the scientific method.

In the case of shotgun experiments, containment reduction has been based on the unwarranted extrapolation of limited data. It is, to say the least, premature to conclude that all eukaryotic genes act through a messenger that cannot be processed in bacteria, and therefore cannot produce harmful products in bacteria. So far, this has been shown for only a handful of genes, although there are a million or so genes in a human cell.

We consider it scientifically irresponsible to jump to conclusions in this way for public relations purposes, when no reputable scientist would make such gross extrapolations in his own work.

The fundamental problem with the guidelines and their revisions is that they have been entrusted to NIH, the sponsor and promoter of progress in biological research, including recombinant DNA techniques, and to its Advisory Committee, which is composed largely of scientists working with recombinant DNA or in closely related fields. A conflict of interest is bound to

occur, for it is only natural that these groups will appreciate the potential value of the work they know so well, and will feel consternation at any contraindication. It is not fair to ask the discoverers and developers of a powerful and exciting new technique to take responsibility for also regulating it.

We have some comments in our paper about the local biohazards committees.

In sum, we would like to make the following recommendations: That the secretary of HEW take control of recombinant DNA activities under Section 361 of the Public Health Service Act, or similar existing authorization; that his control extend to all recombinant DNA activities in this country, including those not supported by NIH or any other government agency; and that he set up an advisory committee including representatives from other relevant agencies such as EPA, OSHA, et cetera. It should include disinterested individuals.

We have some recommendations that the advisory committee review and revise the guidelines in the future, review and approve or disapprove all proposed recombinant DNA projects which have been approved by local committees, and there are a few more recommendations.

MR. LIBASSI: Thank you very much.

We will now adjourn for lunch. It is Nathans,

Anderson, and Nancy Pfund will be the third witness when we return.

We will try to be back at 1 o'clock, promptly, please.

(Thereupon, at 12:05 p.m., a recess was taken until 1:00 p.m., the same day.)

AFTERNOON SESSION

1:15 p.m.

MR. LIBASSI: I think we can begin. I just wanted to make a few comments and observations if I could, very briefly, while we are gathering. One is that I wanted to remind everyone that September 26 was the closing date for receipt of comments with respect to the proposed revised guidelines, so that if anyone wishes to -- who has not made a statement or submitted a statement -- wishes to do so, please do so by that date. If anyone wants to amplify on what they have already submitted, they may do that, and we would be glad to get additional comments from anyone, as long as they are in by the 26th.

I did want to recognize Dr. Jane Setlow, who is the Chairman of the NIH Recombinant DNA Advisory Committee, and not only recognize you, Jane, but also the work of the committee and our appreciation for the extensive efforts that you already have put into this, and the hearings that you all have held, and the time and effort that you have contributed. It is appreciated as part of the way the policy ultimately is made. I want to thank you at this point publicly.

The only other observation I wanted to make was the appreciation for the statements that have been

made already. This is the third hearing of this kind which I have really had the privilege of chairing. One was on the policy for federally-funded sterilizations, which, as you can imagine, was not a subject without some differences of opinion, and that was not only held here in Washington, but in ten regional offices around the country. And then I chaired another meeting on a particular aspect of the welfare law, where again there was considerable controversy between the welfare rights organizations and public interest law groups, and state agencies, et cetera. And now this one.

They all have been opportunities for me to see the level of intensity of feeling, but also the very fine quality of work that has gone into the preparation of the papers, and the efforts that everyone is making to see to it that the government is not only responsive, but also understands, and ultimately comes up with intelligent decisions. So I do want to thank those who spoke this morning and those who will speak this afternoon. Thank you all for the time that you have given to help us do what we finally can say is in the best interest of the country.

Now, why don't we go right to our afternoon session, and we may go for as long as three hours, unless the panel begins to faint on the side here. But if we

can we will go two or three hours, and then we will take a short break, and reconvene if necessary and go another couple of hours, if necessary, to finish.

The first speaker is Daniel Nathans.

DR. NATHANS: For the record, I want to summarize my scientific background and interest in relation to this testimony. I am now Professor of Microbiology and Chairman of the Department of Micriobiology at Johns Hopkins University School of Medicine in Baltimore. I was educated in medicine, specializing in internal medicine, and subsequently I went into microbiology and molecular biology.

For the past 16 years I have taught medical microbiology to students of medicine at Johns Hopkins, and my research, which has been supported by the National Cancer Institute and the Whitehall Foundation, has centered on the molecular biology of tumor viruses. Part of my research involves recombinant DNA methods to study aspects of tumor virus interaction with cells.

I was a member of the committee that in 1973 called for NIH guidelines for recombinant DNA research, and earlier this year I served on the committee that recommended changes in the guidelines dealing with viruses.

The main point of my testimony is that the

proposed revisions of the guidelines are justifiable on the basis of recent experience with recombinant DNA and on the basis of a rational reconsideration of potential hazards of microorganisms containing recombinant DNA. I also believe that the revisions will allow a more natural and creative development of research in those many areas of biology and medicine to which recombinant DNA methods are applicable, resulting in advances that would not occur under the present guidelines.

For example, there are many experiments which now simply are not done because of the restrictions of the guidelines, and in particular I want to emphasize there are many scientists who cannot participate in this research because they are institutions that don't have the appropriate facilities.

I need not recite the experience with recombinant DNA over the past four years. On the one hand, the great promise of the methodology is clearly being realized. And on the other, no single instance of harmful effect has been reported. During these years also, additional instances of natural, interspecies recombination of DNA between microbes or between viruses and cells have been described that make it appear that such genetic interchange is widespread in nature. Therefore, there is now less concern both about the imminent "escape" of an artificial pathogen, and about the novelty of

microbes carrying genes from distant species.

Most of the rest of what I have to say bears on what I mentioned earlier, namely a rational reconsideration of potential hazards of recombinant DNA research. By "rational" I mean related to prior experience.

I think we have had available relevant experience with microbes that was not well utilized in the development of the current guidelines, but is more accurately reflected in the proposed revisions. For example, the experimental evidence that non-pathogenic bacteria like E. coli K12 are not converted into contagious pathogens by simply acquiring small clusters of additional genes, even from donor pathogenic strains. These experimental findings, of course, have been emphasized at the Falmouth meeting.

We have also had very long experience in the safe handling of truly pathogenic microbes. In most cases, simple microbiological methods suffice. For instance, in our medical microbiology course, where we have students of medicine, completely inexperienced in the handling of microbes, we use cultures of Neisseria meningitidis, a cause of severe meningitis; Shigella dysenteriae, the cause of dysentery; Salmonella typhi, the cause of typhoid fever; and many other pathogenic organisms. Over a 16-year period I have not been aware of a single case of disease related to these laboratory

exercises, in spite of periodic spills of these organisms and obvious infection.

This experience also illustrates the well-known fact that so-called "escape" of microbes from the laboratory or infection of a laboratory worker is far from equivalent to disease production, let alone epidemic disease, which is almost unheard of as a result of laboratory infection.

I would argue that a century of experience with safe handling of real pathogens should influence the requirements for handling non-pathogenic organisms containing foreign DNA whose potential pathogenicity is and always has been entirely conjectural.

In regard to viruses, the proposed revisions are based on a similar principle; namely, that as a rule conditions used to work with a virus itself are adequate to work with recombinants containing sections of the viral genome, or even with defective virus vectors. In most instances, I might point out -- in nearly all instances -- the recommendations which are in the proposed guidelines in regard to virus vectors or use of bacteria to clone segments of viral DNA, generally provide for greater physical containment than that ordinarily used to handle the virus itself.

It is difficult to imagine how E. coli K12 containing a segment, say, of SV40 DNA could be more hazardous than the SV40 virion itself. Likewise, defective

SV40 with a foreign segment of DNA is much less capable of spreading in the population than is the intact virus. Moreover, it is now quite clear that each of the mammalian viruses that have been proposed as vectors for recombinant DNA--polyoma, SV40, murine adenovirus, the human adenovirus--readily recombines with its host cell DNA to form a large variety of recombinant viruses. In other words, we appear to be exposed to shotgun-type viral recombinants all the time in our natural environment.

Finally, I would like to comment on the proposed role of the local biosafety committees in monitoring recombinant DNA research. It has always made sense to me, given the assessment of risk, for an institution to carry the responsibility for its own research activities. That is the case, as you know, for other kinds of microbiological research, including the handling of pathogens, and the use of radioactive materials.

From my own experience at Johns Hopkins, I find that the biosafety committee is a serious undertaking there. They do their work diligently. They carry out inspections as required, and their authority is recognized by everyone concerned.

I think the revised guidelines, in specifying the reporting procedures of local biosafety committees to

the NIH, and other types of interchange at the national level and the local level, provide sufficient safety for monitoring the activities, the biohazards committee.

Thank you.

MR. LIBASSI: Thank you.

Carl Anderson?

DR. ANDERSON: My name is Carl Anderson. I am a research scientist in the Biology Department at Brookhaven National Laboratory. I should like to speak to you in favor of the proposed revisions to the NIH guidelines for recombinant DNA.

I have a degree in microbiology, and for the past eight years my research has concerned molecular aspects of the replication of DNA tumor viruses. I operate a P3 facility at the Brookhaven National Laboratory. That facility has been used primarily for handling moderate-risk tumor viruses during the past three years.

Although my experience with recombinant DNA technology is not terribly extensive, I have been involved in cloning specific DNA fragments, and I have been involved in research which has made use of recombinant DNA. I am not now engaged in any specific project involving recombinant DNA, however.

About a year ago I organized a symposium at the Brookhaven National Laboratory which considered the prospects

for the introduction of foreign genes into eukaryotic cells. While that symposium did not in itself directly address recombinant DNA, many of the results and ideas which were discussed at that symposium involved recombinant DNA technology.

I think, therefore, that while there are many areas covered by the guidelines in which I have no direct expertise, I have certain knowledge which allows me to make evaluations of the proposed revisions to the guidelines.

Obviously it is impossible to remove all this from research by regulation or otherwise. In the case of recombinant DNA, we know of no known risks. The guidelines resulted from the thoughts of a group of scientists who were concerned about the potential risks of recombinant DNA. They therefore proposed that these potential risks be considered further before research with recombinant DNA proceeded.

Careful consideration of those potential risks has not, to my knowledge, resulted in any scenario which is likely under the guidelines to lead to substantial risk to the population. It is my belief that the proposed revisions to the guidelines also provide no substantial increase in risk to the laboratory worker or to the public.

On the other hand, they do substantially

facilitate work in the field of recombinant DNA technology. I consequently would urge the committee to adopt the proposed revisions.

More specifically, I would like to speak in favor of the reductions in containment levels for research involving recombinant DNA's containing eukaryotic viral genomes. The arguments that support the reduction in containment level for this area of research are well presented in the report of the Ascot meeting. The prohibitions which are contained in the present guidelines against research involving the cloning of virus genomes resulted from scientists who were about to engage in that work, wishing to hold back because of insufficient knowledge and incomplete reasoning concerning the possible risks in that endeavor.

The Ascot report shows that indeed it is difficult to imagine how a cloned viral genome would be more dangerous than the original virus itself. Many of us have worked for some years with eukaryotic viruses in laboratory situations, and without particular cautions in the case of, say for example, Class 2 agents. We have worked in that fashion without apparent harm.

While common sense dictates that we use good technique in the handling of all virus material, I see no apparent justification for continuing the ban on the cloning

of viral genomes except where a particular risk is involved. I think one can apply similar reasoning to the development of viruses as vectors for the introduction of foreign genes into eukaryotic cells.

Now, clearly, any document can be improved. The guidelines make provision for this improvement, and I believe that the proposed revisions represent an improvement in those guidelines, both in terms of the writing and in terms of facilitating research in this area, and they do so without compromising the public safety.

I think I will conclude my remarks there. I have one other comment that I should wish to make. I don't believe Dr. Norman Arnheim as been able to attend today. He provided me with a statement which I have submitted to the record for you from him, which I brought down this morning, which makes comments similar to those I have just made myself. He is in favor of adopting as soon as possible the proposed guidelines.

MR. LIBASSI: Thank you very much.

Nancy Pfund?

MS. PFUND: Do you all have copies of the testimony, because there are figures in it to which I refer.

MR. LIBASSI: I think we do.

MS. PFUND: Okay.

My name is Nancy Pfund. I am a Research Associate in the Division of Health Services Research at Stanford University School of Medicine. The introductory comments to the revised NIH guidelines by Secretary Califano and Dr. Fredrickson, make specific mention of the need to examine and refine the mechanisms for implementing and enforcing regulatory requirements for recombinant DNA research. In my testimony I will address this issue as it relates to the local regulatory unit, the institutional biosafety committee.

First, I will comment on the importance of the IBC in shaping a representative and efficient regulatory policy. I will then discuss the results of some preliminary data we have obtained on a sample of 30 IBC's. Finally, I will outline some plans for further research designed to fill gaps in current knowledge about the structure and function of IBC's. This research is part of a larger project, of which I am a member, entitled "Medical Progress and the Public Ethical Issues in Biomedical Innovation." This project is funded largely through the National Science Foundation's program in Ethics and Values in Science and Technology.

The latest versions of the NIH guidelines give major regulatory responsibility and decision-making power

to IBC's. Earlier versions of the guidelines focused on the responsibility of the IBC's to implement nationally determined regulatory requirements, and to provide the Office of rDNA activities with the information necessary for making final decisions on research proposals. There has since been a conscious shift toward locating more of the decision-making power at the local institutional level. Newly mandated activities, such as approving the initiation of certain proposed rDNA experiments, considering and acting upon requests for approval of single-step reductions in containment levels for experiments with purified DNA and characterized clones, and participating in the development of emergency plans for accidental spills and personnel contamination represent significant scientific and social responsibilities.

To fulfill these larger functions effectively, local biosafety committees must be procedurally sound and broadly representative.

While the revised guidelines present a more explicit outline for IBC composition than did the original guidelines, the wording is still general enough to permit great variation in the structure, and hence, in the function of these committees. The present composition of IBC's, the representation of groups such as recombinant DNA scientists, scholars in other fields,

health and safety personnel, workers, and members of the public remains largely unknown. Yet, such information is essential in assessing the current operation of IBC's and in improving their future function.

I would like to share with you our research results, which illustrate the importance of collecting information on IBC's.

Data for preliminary analysis of the membership composition of 30 of the approximately 150 IBC's throughout the country were obtained from the Office of Recombinant DNA Activities by Michael Maniates and Pamela Lippe, of Friends of the Earth, and by Philip Bereano at the University of Washington. These 30 IBC's were selected on the basis of available data. They represent research institutions as well as public and private universities, including many of the institutions receiving the largest NIH grants for recombinant DNA research -- universities like Stanford, UCSF, MIT, et cetera.

Biographical data were collected on all committee members, along with their professional field and their relationship to the given institution. In order to assess the representation of different types of members on these IBC's, individual committee members were assigned to one of nine categories. The categories attempt to distinguish direct or indirect involvement in recombinant DNA research,

and also the nature of members' affiliation with the institution.

The nine categories were defined as follows: First, scholars in fields such as microbiology, biochemistry, or molecular genetics were categorized as scientists in the recombinant DNA disciplines. This category includes individuals most likely to be directly involved in recombinant DNA research, and represent this professional viewpoint.

Next, scholars in fields which may be related to recombinant DNA research, such as biology, chemistry, medicine or engineering were categorized as peripherally related scientists.

The third category represents related administrators, and includes institutional and non-institutional officials who are involved in an area related to recombinant DNA, either in research affairs or in health and safety enforcement. These latter two categories include individuals whose professional training may have been related to recombinant DNA activities.

The other major categories included non-related scholars, non-related administrators, public representatives, workers, and students.

Now, if you look at Figure 1, you see the

distribution of IBC's by size. Sizes range from 3 to 19, with an average size of just over 10. Committee sizes also varied by type of institution. Universities tended to have somewhat larger panels than non-educational institutions did.

Biographical data indicated that the committees were made up overwhelmingly of men. Also, most committee members, over 90 percent, were directly affiliated, in one way or another, with the university or research institution.

The representation of different types of members on IBC's is shown in Figure 2. The pie-shaped figure indicates the membership composition of a typical IBC -- a typical committee, the average number of members per committee in each of the nine membership categories. Not surprisingly, scientists in recombinant DNA disciplines represented the largest membership block. The representation of recombinant DNA-related members is broader still, averaging close to 85 percent if you include peripherally related scientists and administrators.

The proportions of public members, workers, non-related administrators and students each averaged less than two percent. Likewise, the representation of non-related disciplines was small. On the average, only nine percent of the committee members were scholars in disciplines unrelated to recombinant DNA.

In short, the number of committee members who may be considered non-experts in rDNA research is very small.

A similar picture emerges from examination of each membership category in the IBC's. All 30 committees had at least one scientist in a recombinant DNA discipline, and ten percent, or three of the committees, contained only recombinant DNA scientists. Related administrators and peripherally related scholars were each represented on about 60 percent of the IBC's in the sample. The percentage of committees with members from the non-expert categories was much smaller. In fact, more than 70 percent of the IBC's surveyed had no representation at all of students, public citizens, workers, and non-related administrators, respectively. Overall, most of the IBC's in the sample included a limited number of different types of members.

With these data one can also examine the relationship between size of committee and breadth of representation to see whether or not larger committees result in more diversified representation. Figure 4 shows the average number of membership categories represented in committees of different sizes, and indicates that up to a size of about ten members, breadth of representation did increase with size. Beyond ten members,

however, the average size of IBC's in this sample, the number of membership categories represented did not increase.

Finally, the relationship of committee size to representation of non-expert and non-institutional members is shown in Figure 5. The average percentage of recombinant DNA scientists on committees declined sharply with decreasing committee sizes, up to ten members, after which it levels off at about 50 percent. The representation of institutionally affiliated members, on the other hand, is essentially unrelated to committee size, averaging from 90 percent to 100 percent, regardless of the number of members. This indication of minimal representation on IBC's of non-institutionally affiliated individuals may be an important policy issue if it is associated with the lack of responsiveness to local community concerns.

From the information I have described, it is clear that extensive public or even non-scientific input on IBC's remains the exception rather than the rule. The increased specificity of public and worker representation requirements in the revised guidelines may improve future opportunities for such input. However, as suggested by the pie-shaped diagram, individual committees currently contain so many science-oriented or in-house members, that

even the mandatory presence of a public representative as required in the new guidelines may have only a limited effect.

Unfortunately, little is now known about the selection process for public and worker representatives, and it is not specified in the new guidelines. Thus, the degree to which these members represent a constituency or merely reflect administrative decisions already made at the institutional level remains uncertain.

To provide information on these and other issues concerning the IBC structure and function, the project at Stanford, of which I am a member, plans to undertake a two-stage research process. First, a survey will be conducted of all 150 IBC's to obtain information on the selection process for IBC members, the process and content of committee deliberations, the level of public participation in committee activities, and the degree to which IBC's are concerned with safety training and health monitoring. And you have a mock up of the questionnaire enclosed in your materials.

The second phase of this research will obtain more detailed and qualitative information on committee functions and individual members' attitudes toward committee organization and actions. This phase will utilize selective interviewing and case studies of

individual IBC's. It is our hope that results will contribute to a recombinant DNA research policy that takes into account the many aspects of committee structure and function which influence the operation of IBC's and their openness to various views. With such information, future recombinant DNA regulatory policies, specifically those which expand the responsibilities of IBC's, could draw on fact, not assumptions about the effectiveness and efficiency of this method of regulation.

I would urge that the NIH and the HEW endorse and support such a study.

Thank you.

MR. LIBASSI: You are not suggesting, however, that we make no changes pending the completion of your study?

MS. PFUND: No, I think that within future iterations of the guidelines there should be a mechanism to include information about the efficiency of the regulatory structure.

MR. LIBASSI: Thank you.

Donald Brown?

DR. BROWN: My name is Donald Brown. I am a medical doctor. I have done biology on microorganisms, and on animal genes for the past 15 or 20 years. I have been involved in the discussions of recombinant DNA research

from the very beginning, including work on the original Asilomar Committee, which dealt with the potential -- the possible hazards of eukaryotic genes.

I am here to support the revised guidelines as a move toward rational guidelines, although it seems to me that they are not all the way at rational guidelines.

Several years ago the strict NIH guidelines were issued, and many of us who had been involved in this proceeding from the beginning had very grave misgivings about our participation in this process. We had suggested that recombinant DNA research go slowly, and had even proposed that some experiments not be done at all. Yet, there was no evidence, not the slightest bit of evidence, to fear even these forbidden experiments at that time, nor is there any evidence today.

Yet scientists involved in the work were ready to limit themselves while they took stock of a new and powerful method. Now, this was a process, it seems to me, of self-education in which scientists wanted to think about this process for a while. In retrospect, we should have realized that the public statements of uncertainty by scientists, and the ensuing publicity were absolutely guaranteed to generate opponents -- which you have heard many this morning and this afternoon -- of recombinant DNA, and the controversy that followed was guaranteed, in

turn, to generate strict rules for this research.

Like many scientists, I have made myself available to citizens' groups, and we have had many informal discussions of recombinant DNA over the years, and the controversy. And there is always the implicit assumption amongst lay people that there must be something dangerous in recombinant DNA, or otherwise, why all this publicity? Why all this fuss? Why have so many people spent so many hours of their time working out these guidelines and these rules?

In fact, every new, more strict guideline, every response to the demand for more safety really makes the public more fearful, because then that simply assures them that there must be something really dangerous about this research.

The fact is, though, that the vast majority of informed microbiologists, public health specialists geneticists, and experts in the field, who have really considered the dangers of recombinant -- the supposed dangers of recombinant -- DNA have come to feel that there is negligible risk of producing a dangerous bacteria in the laboratory by accident. And the existing NIH rules are really exceedingly strict. I would like to somehow explain to you what I mean by that.

These existing NIH guidelines have really slowed

and limited recombinant DNA research. There is no question about that. Aside from the great expense of the required physical facilities and the enormous amount of bureaucratic work that has to be overcome and applications that have to be filed, even for the exchange of something which has been called "characterized" and "free of harmful genes," requires enormous numbers of applications and very special conditions. But this is minor compared to the fact, in my mind, that certain kinds of experiments have not been possible to do because of the existing guidelines, or, if they have been able to be begun, they have begun very slowly.

I am thinking particularly of recombinant DNA research with viral and human DNA. We are faced with the extraordinary paradox that it is considered safer to study a living virus that is known to be infectious than it is to put one or more of its genes inside the harmless bacteria, E. coli. If we were rational, we would in fact encourage the use of viral genes recombined in bacteria as a means of biological containment.

Although no viral DNA cloning has been permitted, the advent of these disabled vectors has permitted the beginning of human DNA experiments. It seems to me that these are two very important research areas in biology which must be pursued for the benefit of mankind -- that is,

the understanding of human genes and the characterization and study of viral genes.

I said at the beginning that I have had very grave misgivings about this experience and these rules. However, what I most feared has not happened. I imagined that once the NIH guidelines or rules were set down, they would be fixed forever and would never be revised. Forgive me for my lack of faith in this regard, because these revised guidelines show a tremendous amount of very rational and sensitive thought by a lot of people, and I am extremely impressed by the thought and time which has gone into it.

There are still features of them which I consider to be unnecessarily strict; the use of disabled vectors, in some cases, for the shotgun experiments in warmblooded animals is one such example.

I particularly am impressed by the delegation of more responsibility to the local institutional biohazard committees. I was deeply depressed just one minute ago when the person who preceded me seemed to equate every biochemist and molecular biologist with someone who studies and has a vested interest in recombinant DNA. That sector on the graph looks as though people working on recombinant DNA are essentially the people of the earth. I must say that I do believe that people who do recombinant DNA research and have a vested

interest should not be part of these committees. However, I am also a member of the public, and I would feel much more comfortable to know that there are scientists and epidemiologists, and biochemists who know something about recombinant DNA research who are making the decisions. Therefore, I think that scientists should be an important part of these institutional biohazard committees.

Furthermore, it seems to me that the rules are set forth in such detail that I have very little worry about the uneven interpretation of these rules by different committees.

I also like, I might say, the fact that there is now opportunity for case-by-case review of those things which don't fall into the general framework covered throughout the body of these revised rules.

In general, I think the revised guidelines are therefore excellent, and I really hope that they will ultimately be revised right out of existence, and that someday, as they should be, people who work in recombinant DNA will be able to use just the established microbiological procedures -- those that really fit the potential problems of recombinant DNA -- which, it seems to me, more and more people are realizing are negligible.

Thank you.

MR. LIBASSI: Thank you.

Francis Ruddle?

DR. RUDDLE: My name is Frank Ruddle. I speak for no organized group, but mainly for myself. I am a cell biologist and a geneticist, and I have been a faculty member in the Department of Biology at Yale University since 1961, in which I now serve as Chairman.

At Yale I served previously as Chairman of the Biological Safety Advisory Committee, which regulates recombinant DNA research at our university. I am proud of the fact that the City of New Haven is actively represented on that committee, and has been from the outset, and that all of our meetings have been, from the outset, advertised and open to the public.

I should also like to mention that there is, to my knowledge, no opposition within the university or the City of New Haven today to the implementation of the revised guidelines. I will come back to this point in a moment.

My professional interest is in somatic cell genetics. This discipline is concerned with an understanding of the genetic organization and function of mammalian chromosomes, especially those of man. An important technique in my study is cell hybridization, which permits one to literally fuse mouse and human cells to

produce viable, healthy hybrids, which can be propagated in tissue culture.

It is interesting that some would argue that there is a biological risk associated with this process, which is unrelated to recombinant DNA techniques. But I would like to point out that these kinds of experiments have been going on in hundreds of laboratories since the early 1960's without any indication of risk.

In such hybrid cell populations, one can trace the loss of human chromosomes and correlate that loss with particular human traits. In this way it has been possible to use hybrid cells to map human genes to particular human chromosomes. Since 1970, more than 200 genes have been mapped in man using this technique in a number of laboratories. The basic knowledge gained has contributed to our understanding of primate evolution, the mode or action of gene mutations which result in specific genetic abnormalities in man. And to cite a specific case, these studies have resulted in a better understanding of the genetic control of the interferon system, which is instrumental in protecting organisms, including man, from viral infection, and which shows promise as an anticancer therapeutic agent.

Also, a great deal of information has been provided on many other interesting and important biological

systems.

Until the advent of recombinant DNA technology, the somatic cell genetic technique could only analyze the human genetic material at a relatively low level of resolution. Making use of recombinant DNA procedures, it is now possible to continue the study of human genetics at a very high level of resolution. It is like comparing the light microscope to the electron microscope.

Using nucleic acid hybridization techniques, our laboratory in collaboration with an NIH research group, has recently mapped the human genes for alpha and beta globins. This knowledge now provides new possibilities for experiments dealing with a better understanding of the control of hemoglobin expression with obvious relevance to genetic, developmental, and environmentally induced abnormalities involving human hemoglobins. We are now beginning to use cloned -- that is, recombinant -- cloned material -- globin DNA sequences -- for this purpose, a method which is far simpler, faster, more reliable, and cheaper than those previously employed.

It should also be strongly emphasized that many biologically important human genes will be mapped in man only -- and I would like to emphasize "only" -- by using recombinant DNA technology in concert with the somatic cell genetic procedure. There have been statements

made that all of the advances which stand to be made could be made by other means, and I don't think that is entirely correct.

There is no question in my mind that our understanding of human genetics and development depend importantly on the use of recombinant DNA methodologies. It also follows that the reduction of containment of human and mammalian DNA, particularly human, to PK2-EK2 from P3- or P4-EK2 will make a huge difference in our rate of progress in human genetics.

There is another scientific development which is pertinent to our deliberations here today. Recent experiments performed at Columbia University have shown that it is possible to transform mammalian cells -- that is to say, introduce functional genes into cells -- by simple exposure to mammalian DNA. This will provide a means of purifying particular kinds of human genes using DNA-mediated transformation as a bioassay. Alternative techniques for achieving the same purpose make use of deleted animal viruses such as SV40.

It is clear to all -- that is, in the profession -- that the availability of cloned mammalian genes will provide a very great impetus to our knowledge of the human gene map -- that is, human genetic mapping -- and the control of expression of human genes. Also, the isolation

of human genes by cloning represents the first step in pharmaceutical production of therapeutic products such as insulin, blood clotting factors, interferons, and a host of additionally medically-important products.

The rapidity with which such products become available to the public will be significantly influenced by the stringency of the recombinant DNA guidelines. It seems ludicrous that some of our most productive and creative scientists have felt it necessary to carry out their investigations in Europe, because of the unrealistically stringent regulations here at home.

This practice, if continued, will only serve to weaken United States biomedical science. Certainly the reduction of containment levels for eukaryotic cells and for animal viruses is very much in order.

There is one additional point I would like to make. In connection with the transformation experiments which I mentioned earlier, in that connection, we have been isolating in our laboratory a small segment of the Herpes simplex virus chromosome, containing a particular gene. We are forced to do this now by growing up large quantities of the live virus. The practice is expensive, time-consuming and cumbersome. We would prefer not to deal with large amounts of live virus, because of the risk of possible exposure to laboratory personnel. It would, of course, be

possible to clone the herpes chromosome segment of interest using existing recombinant DNA techniques. Such a practice would be far simpler, faster, and cheaper than growing the intact virus. From a biosafety viewpoint, I would judge the recombinant DNA cloning of the herpes fragment to be, in itself, innocuous, and certainly far safer than growing the virus. This kind of cloning experiment is not currently possible at P3 levels of containment under the provisions of the existing guidelines. It could be readily done under the revised guidelines.

In closing, let me say a few words about the biological risk. Our Department of Biology at Yale covers a broad spectrum of the biosciences, ranging from molecular biology to the environmental sciences. None of my faculty members have expressed concern over these pending revisions of the recombinant DNA guidelines. Throughout the whole university, including the school of medicine, there is in fact broad and strong support for the implementation of the revised guidelines.

I believe we should not lose sight of the fact that the risk associated with recombinant DNA organisms has not been established, much less measured or quantitated. On the other hand, the risk of disease, aging, birth defects, is well established and altogether too real.

Recombinant DNA technology can contribute in a major way to our understanding of basic biological phenomena, and this knowledge in turn is bound to provide practical ways of dealing with very real medical problems, the very real medical problems of mankind.

I believe that the implementation of these new revised guidelines is in the best interest of the public, and that they should be approved at the earliest possible time. I personally endorse them wholeheartedly.

MR. LIBASSI: Thank you very much.

Myron Levine?

DR. LEVINE: Thank you.

Ladies and gentlemen, I am speaking as an individual who has been involved in clinical research, including clinical research involving recombinant organisms. My current position is as Director of the Center for Vaccine Development at the University of Maryland School of Medicine, where I hold an appointment as Associate Professor of Infectious Diseases.

Two points I would like to make ladies and gentlemen. One is that I feel the risks of preparing a pathogen advertently or inadvertently by recombinant DNA methods is miniscule, and I would like to point out some reasons why I believe this is so. Secondly, I would like to urge that priorities be reset with respect to

where we should have concern regarding various types of pathogens.

In 1970, as an individual in the Commissioned Corps of the Public Health Service, I was assigned to the Shigella vaccine development program at the University of Maryland, where various Shigella dysenteriae vaccines were tested. These were in the early years -- organisms that were prepared by recombining genetic material between virulent Shigella organisms and E. coli. The work was based on findings of Dr. Formol at the Walter Reed Institute of Research. Dr. Formol was able to identify the steps involved in the pathogenesis of dysentery, and was able to actually identify the genes within the Shigella. Since E. coli is a first cousin of Shigella, he was able to transfer the homologous genetic material from E. coli into the Shigella germs. These recombined vaccine strains were fed. Of six different vaccine candidates fed, two were attenuated in individuals, and in healthy adult volunteers, and were well tolerated for or associated with some adverse reactions. The adverse reactions, though, were milder or no different than a dysentery syndrome were virulent organisms fed.

In more recent studies, the reverse has been done. The surface coverings of Shigella, what we believed

were the protective antigens, were transferred from Shigella dysenteriae organisms into E. coli by Dr. Formol; and these E. coli carrying the Shigella genes were fed to adult volunteers in very high doses, as high as ten billion organisms, with proliferation, and there were no adverse effects whatsoever.

In other studies, even more recently, we have for a number of reasons attempted to determine the virulence properties that certain E. coli have -- E. coli that cause traveler's diarrhea. Most of these studies were carried out, not by myself but by Drs. Hornick and DuPont in the same division some years ago.

In these studies, attempts were made to transfer the enterotoxin, the diarrhea-causing toxin, from E. coli that produced traveler's diarrhea into an E. coli that was cultured from a healthy individual, in the naive assumption that just transferring this one virulent property would result in a pathogen; and this organism with the transfer toxin was fed in high doses, and no illness occurred, and there was minimal proliferation. That was the first suggestion that we can't make a pathogen if we want to.

Subsequently, additional virulence properties were put into E. coli. These were studies done about five or six years ago, and still there was no evidence that man

could in the laboratory produce a pathogen, even if he wanted to.

I see great uses for recombinant DNA with respect to preparation of certain vaccines in enteric diseases. Right now, the brightest hope for preparation of a vaccine against the E. coli that causes traveler's diarrhea is to purify the colonization factor pili, the hairy little organelles on the surface of the bacteria. This is very difficult to do. By use of recombinant DNA the possibility exists that the cloning of the appropriate genes could allow large amounts of this antigen to be produced and a vaccine prepared in a much more cost-effective manner.

Similarly, now that much is known about the subunits of the enterotoxin, it is possible to separate the toxic portion from the binding portion, theoretically, and by use of cloned genes to prepare just the binding portion.

So for these reasons I have attempted to point out that pathogens have had tens of thousands of years to develop, and it is highly, highly unlikely that man can put together a pathogen in a cookbook fashion. Evidence in the past few years has suggested that this is so.

The last point I want to make is that I am much more worried or bothered by known pathogens that are worked with in laboratories. Last week we saw that smallpox virus

-- virulent smallpox virus, Vireola major -- escaped from a laboratory in England and infected someone, resulting in a death. There are virulent viruses and other agents -- known virulent viruses -- that are worked with in the United States with far less concern, far less inhibitions, administrative constraints, et cetera. I personally would rather see the priorities set to grade containment of those viruses that are worked with. These would include, as an example, influenza viruses.

Thank you.

MR. LIBASSI: Thank you very much, Dr. Levine.

Marshall Edgell?

DR. EDGELL: My name is Marshall Edgell. I am a Professor of Bacteriology at the University of North Carolina.

In my opinion, the proposed guidelines represent a small step in the right direction, but only a tiny step. I have had difficulty from the very beginning in gaining any intellectual comfort from these guidelines on recombinant DNA inquiry. The bulk of the public argument, as I have seen it, revolves around trying to solve this social calculus of balancing the quality of the conceivable miracles against a magnitude of the advertised dooms.

A complex society such as ours would be negligent

to turn its attention away from the consequences of our actions. But these actions involve more than just the ends. In this social calculus it could be just as disastrous to ignore the means established as to ignore the possible ends.

We have had extensive historical experience at what happens when a society begins to embrace the posture of the ends justifying the means. Guidelines restricting intellectual inquiry are clearly a serious business. The Russians experimented with protecting their society from inquiry into the genetics of inheritance. In that case the action was simply an extension of a policy already accepting the ends justifying the means. Having once accepted this tenet, it is not so easy to retreat.

If there were a bona fide biological hazard associated with these experiments, it would be foolish to ignore them under the guise of the freedom of inquiry. Such freedoms have never been a license to maim. This tension between the desire for freedom and the security needs of us all has been resolved in the past. While there continue to be details that need resolution, the basic structure of the solution is exemplified in how we deal with freedom of speech. That is, the freedoms are given the benefit of the doubt until breached by either social consensus or by overwhelming

documentation. This posture has served us well in the past, and it should require an exceptionally strong case to bring us to a different position.

Only a scientific hermit could label the current condition one of consensus. We also seem slightly deficient in overwhelming documentation of hazard.

I suppose it is the province of politics to resolve tensions in such a case. However, I see no reason to withdraw the benefit-of-the-doubt policy afforded our important freedoms in the past.

I don't believe the major issue revolves around the potential benefits versus the potential costs measured simply by comparing miracles and disasters. Nevertheless, I can't resist commenting on the miracles. It seems to me we underestimate them. Futurists seem singularly unable to lay out for us the panorama of the future rooted in the discoveries of the present. We consistently underestimate the future by predicting that it will be the sum of the projection of today's trends.

It is the unexpected discoveries which seem to characterize the futures that we have already known. How can we project the trends of the presently undiscovered? While the grail of human insulin seems today a splendor indeed, I don't think that that is the major harvest to be anticipated from recombinant DNA inquiries. The harvest,

in my opinion, will be a vast realm of unknowns becoming known. It just isn't true that this realm has many doors which could be as easily entered. The recombinant door has been opened for us already, and it is the only door open now. Maybe there will be other doors, by maybe not. What will be the cost to those who could have been helped, but weren't?

I sympathize with those who see uncertainties in such a future. What is the security in all these unknowns? But for all the nostalgia, do we truly want to go back, or even stay here forever? It is true that today's technology has carried with it a cost. However, I for one, find coping with saccharin considerably more tolerable than enduring polio.

I find the guidelines for recombinant DNA inquiry an intellectual outrage. These new guidelines seem to me the tiniest of steps in the right direction. Only the strongest of documentation should persuade us to avoid such a token.

Thank you.

MR. LIBASSI: Thank you very much.

Oscar Miller is the next speaker.

DR. MILLER: My name is Oscar Miller. I am Professor and Chairman of the Department of Biology at the University of Virginia. As a current non-user of

the techniques being discussed here, I would like to briefly comment on the proposed revised guidelines from three points of view: in my capacity as chairman of a department in which recombinant DNA research is ongoing; in my capacity as head of an institutional committee charged with evaluation of the need and feasibility for P3-level physical containment facility; and as a colleague and friend of many of the scientists involved in the use of recombinant DNA techniques to study the structure and regulation of genetic activity.

As chairman of a department containing faculty members interested in using recombinant DNA techniques, I have an obligation to foster conditions that will advance the careers of such faculty, but I also have a higher obligation to ensure the safety of all the personnel of my department from biohazards of all kinds. As it became evident that recombinant DNA techniques would be powerful experimental probes, we early on held open departmental meetings to discuss the pros and cons of the use of such techniques.

After careful consideration of the original guidelines and conversations with trusted, knowledgeable colleagues in the field, I became convinced that the recombinant experiments being proposed by certain members of my faculty would be safe if carried out under the

conditions required by the guidelines. To this end, I supported the appointment of an institutional committee on recombinant DNA research, responsible for the approval and monitoring of physical containment facilities, and the experiments done therein.

The committee as appointed at Virginia contains, in addition to knowledgeable basic biological scientists, representatives from the areas of city and county government, science, law, and epidemiological medicine. Similar knowledgeable and broad-based representation is characteristic of analogous committees at other universities with which I am familiar, indicating to me that institutions and their scientists are acting in a highly responsible way to the need to safeguard communities, while at the same time allowing valuable recombinant DNA research to continue.

The responsible records of local committees in implementing the current guidelines argues well for their abilities to assume increased authority under the revised guidelines in a manner that will continue to assure safety from potential biohazards for those living in their communities.

Since members of my department were interested in carrying out research using recombinant DNA techniques, I was asked by my institution to form a special committee

to evaluate the need and feasibility for P3-level physical containment facilities. The need and feasibility for a facility was soon established, and a successful proposal for matching funds was made to NIH. A three-member users committee was proposed to oversee the actual day-to-day operation of the facility, with this committee to be closely monitored by the institutional committee. Again, my interactions with the institutional committee in my endeavor to obtain a P3 facility reinforces my strong belief that such committees will continue to responsibly carry out their assigned duties under the revised guidelines.

I have the pleasure of knowing many of the scientists who are carrying on highly significant research projects using recombinant DNA techniques, some of whom have been involved in the formation of the original guidelines and the current proposed revised guidelines. I count several of these investigators as very good friends. As a group, they are highly motivated, highly intelligent, and intellectually honest scientists, who are respected in their communities. I find, perhaps not unexpectedly, that they are also quite gentle people.

In addition, those whom I have been privileged to know in family situations have always demonstrated a deep affection for their spouses and their children. Knowing these people as I do, it is inconceivable to me

that any of them would put rapid career advancement made possible by unsafe, biohazardous techniques ahead of their concern for the safety of their families and communities. I have the highest respect for the intellectual and moral honesty of these scientists, and their considered study and approval of the revised guidelines is, in my opinion, the strongest recommendation for their adoption.

Thank you.

MR. LIBASSI: Thank you.

Charles Emerson?

DR. EMERSON: My name is Charles Emerson. I am Associate Professor of Biology at the University of Virginia. I would like to read a brief statement in support of the adoption of the revised guidelines for recombinant DNA research. This statement was prepared by myself and Dr. Michael Kuehl of the Department of Microbiology, and reflects not only our own views, but those of Drs. Robert Grainger and Robert Devlin of the Department of Biology, and Drs. Thomas Parsons, Carolyn Collins and William Steinberg of the Department of Microbiology at our institution.

We are molecular biologists whose research programs are focused on understanding the mechanisms of gene regulation in higher organisms. Specifically, we are studying a variety of problems which include, for example,

the molecular basis of gene regulation during embryonic development of avian and human muscle, genetic control of antibody formation, and expression of tumor viruses in avian and mammalian cells. Our research programs have been and will continue to be profoundly influenced by the information and ideas resulting from recombinant DNA research and will be greatly affected by any guidelines imposed upon this area of research.

We agree that the current guidelines, which have imposed stringent regulations on experiments involving recombinant DNA technology during the past few years, were appropriate. This period of extreme caution has served a useful function of permitting a thorough evaluation of the potential risks of such experiments. However, despite efforts by scientists, environmentalists, lay people, et cetera, to conjure up worst-case scenarios of potential hazards, there is no evidence to support the contention that recombinant DNA research poses a biohazard to humans or their environment. Arguments that biohazardous organisms may be produced through recombinant DNA research appear to us to be simply speculation with no basis in fact, and no foundation or understanding of basic biological processes.

In view of the lack of evidence for creation

of significant biohazards through recombinant DNA research, the lowering of physical containment requirements in the proposed revised guidelines is entirely appropriate. In addition, the revised guidelines can expect to have considerable positive impact on recombinant DNA research in this country. This is an issue to which we can speak from our own research experience.

The current guidelines have imposed stringent physical requirements, P3 or P4 physical containment, for studies involving higher organisms, such studies as the one at our university. The requirement for these extreme levels of physical containment have made it difficult and, in many cases, impossible to use this important technique for studies of genetic material from higher organisms. P3 facilities are costly to construct and to maintain, and at many institutions, including our own we have not had, during the past, resources to establish such facilities.

In my own case, I have undertaken some recombinant DNA experiments at a P3 facility located at another institution a considerable distance from Virginia. As a result of the enormous complications and inconveniences of this arrangement, my research program has been set back at least a year.

On the other hand, Dr. Kuehl and our other colleagues at the university have not even attempted to

use these recombinant DNA techniques in their research because of the lack of a P3 facility at Virginia, in spite of the importance that these techniques would have for their research programs.

The proposed guidelines are a conservative step in relaxing the requirements for physical containment for recombinant DNA research. However, adoption of these revised guidelines will serve the dual purpose of continuing to greatly minimize the possible risks of recombinant DNA research, while at the same time providing conditions which will permit the realization of the huge benefits which will derive from this technique.

Thank you.

MR. LIBASSI: Thank you very much.

Richard Hartzman?

MR. HARTZMAN: My name is Richard Hartzman. I represent Friends of the Earth in the lawsuit which is mentioned in the Environmental Impact Assessment, and I am here today on behalf of Friends of the Earth.

The major point I wish to make today concerns compliance with the National Environmental Policy Act, which I will refer to as NEPA. Now, I think we have heard today a real difference between viewpoints expressed this morning and viewpoints expressed this afternoon on some of the scientific issues. What is apparent to me is

that there is still a great deal of controversy, and I see NEPA as the ideal tool, or the best tool that we have available today, to resolve these controversies, to really address them objectively and forthrightly.

Now, NEPA requires the preparation of an Environmental Impact Statement for all major federal actions which could significantly affect the human environment, and it requires that such a statement be prepared before taking any action. The CEQ guidelines and extensive HEW procedures in Chapter 30 of the General Administration Manual of HEW govern NEPA compliance.

NEPA is a fundamental environmental law which provides the only mandatory, formal mechanism for technology assessment. It also provides for public input in government decisions affecting the environment. The basic idea underlying NEPA is: Think before you act, tell everyone what you are thinking, and act wisely.

From the beginning of the recombinant DNA program at NIH, only the most feeble effort has been made to comply with NEPA. The final Environmental Impact Statement on the 1976 guidelines came out over a year after the guidelines were promulgated. The excuse that the guidelines were urgently needed does not exist with respect to the revisions now being considered, and the efforts of NIH thus far constitute a failure

to comply with NEPA. First of all, a thorough Impact Statement is clearly required by the law. The revisions are both major and significant, and the direction of the changes will mean an increase in the possibility of affecting health and the environment. The comprehensive lowering of containment standards, the exemptions. the possibility of exceptions to prohibited experiments all contribute to an increased risk to the health and the environment.

The changes will lead to a significant expansion of recombinant research in addition to reduced safeguards, and there are several hundred experiments in this country now which will be affected. Moreover, the revisions will have worldwide impact on guidelines being used in Great Britain, the European continent, Japan, Israel, Australia, likely even the USSR. Even a casual perusal of HEW regulations and CEQ guidelines demonstrates the necessity of a full Impact Statement for the revisions.

Now, I will just give a couple of examples. Again, I already made mention of the controversy surrounding the scientific issues with respect to the guidelines. Now, the CEQ guidelines and supporting case law say when there is such a substantive controversy, that there must be a full Impact Statement, and

environmental assessment is not sufficient. Also, NEPA requires that alternatives be considered. Well, Dr. Whelan this morning stated that the different national guidelines have strikingly different containment requirements for the same organisms. This has not been explored at all, and no justification has been given for choosing the particular containment standards set out in the guidelines.

Also, there has been very little mention from an environmental standpoint about the activities of the Department of Agriculture and their great interest in recombinant DNA techniques. Now, here I see more clearly environmental impacts coming out, because you are talking about agricultural products and a desire to release these new organisms into the environment. I think these directions should be explored in an Impact Statement. This is where NIH is a lead agency. The Department of Agriculture should provide input into the NEPA process in developing a full, thorough Impact Statement.

My second point concerns the Environmental Impact Statement [Assessment]. This is just a pro forma document. It is full of conclusory, self-serving assertions, and contains essentially no analysis. The prime example of the lack of analysis is on page 33110, where the basis for exemptions is given. I will read from the document:

"Under the first exemption, experiments with recombinant DNA molecules that are not in an organism need not be subject to the guidelines. This is based on the safety of these experiments." That is the analysis of the rationale for the first exemption.

One of the things that is really troublesome in this Assessment is that mostly it is just a reprint of the Director's Decision, probably 90 percent of the 40 pages. It looks bulky, but there is really very little of an assessment in it. But in the language from the Director's Decision, it mentions the first exemption, and says, "This is in recognition that naked DNA, which is rapidly inactivated in nature, is extremely unlikely to be hazardous."

Now, there has been controversy and debate on that point this morning. It needs to be explored, and it needs to be explored in an Impact Statement.

I could go on with the other exemptions, but the level of analysis is similar. They say, well, this is based on occupational safety and the environment, but it doesn't say why. It doesn't give any kind of either scientific judgment or experimental data for it.

There is a lengthy discussion of E. coli in which a number of issues are not at all addressed in the Environmental Assessment. Also, there is

discussion of the Falmouth Conference in the Environmental Assessment, and Dr. Gorbach's letter is quoted. But no mention is made of the letters from Drs. King and Goldstein and Levin, which also addressed the Falmouth Conference and take a different view, and say that any relaxation of the guidelines is premature at this point. And those very letters were published in another document put out by the NIH--in the Recombinant DNA Technical Bulletin--but it is not mentioned in their Assessment.

Also, there is almost no discussion of other organisms. While we have page after page going into E. coli, E. coli K12, very little, if nothing, is done with respect to other organisms, and the guidelines definitely contemplate the use of them. Some are now being used -- Bacillus subtilis, I believe. There are at least a couple of experiments under way using that as a host organism, and others.

Now, as to my recommendations, I feel that it is important to proceed with the promulgation of changes in procedural and administrative sections of the guidelines. That would be Part I and Part IV, and Section II-D, which concerns certification of host-vector systems. I think there is a need to improve regulatory mechanisms and create flexibility in the recombinant

program. Of course, there have been a lot of suggestions made for changes in those sections, and I will make a couple of my own in a minute.

However, it is premature to make any changes concerning containment and the actual guidelines. First of all, there has not been an Impact Statement done, and this needs to be done before any action is taken on a significant environmental action of this nature. Secondly, there has not been a convincing case for relaxation, and I don't feel there is sufficient confidence at this point. I will just point to one comment which is made both in the Director's Decision and in the Environmental Impact Statement. The Director says that the containment standards, the classification may appear somewhat arbitrary in the decision document. When you turn to the Impact Assessment, it says that it <u>is</u> somewhat arbitrary. Now, I would like to know which one it is, as a member of the public.

I will go to one of my recommendations. In Part I, there is no provision providing for higher containment or new prohibitions. Now, there might be unperceived hazards which will arise, and some mechanism must be available to act in case they do. There is nothing. There is a mechanism for decertification now, but not for higher containment or new prohibitions, and I will submit some

language for that.

Thank you.

MR. LIBASSI: Thank you. If you have additional comments to make that you did not get to read -- is your statement with us?

MR. HARTZMAN: It is just in notes at this point. I will write it --

MR. LIBASSI: If you could just drop us a letter with any other additional comments, we would appreciate getting them.

MR. HARTZMAN: Certainly.

MR. LIBASSI: Thank you.

David Coplin?

DR. COPLIN: My name is David Coplin, and I am Assistant Professor at the Ohio Agricultural Research and Development Center, which is the experiment station for the Ohio State University. I am also a member of the American Phytopathological Society's Committee on Recombinant DNA. My training is in both bacteriology and plant pathology. I am currently working on the genetics of plant pathogenic bacteria.

As a plant scientist, I am concerned that the genetic studies on plants and plant parasites have been delayed under the present 1976 guidelines for recombinant DNA research. I will be commenting on the guidelines

today from the viewpoint of a plant pathologist.

Each year plant diseases -- the cost of plant diseases in this country is very high in terms of crop losses and the expense of control measures. Due to concerns for our environment and the public safety, many pesticides have been taken off the market, and relatively few new ones are taking their place. This situation increases our need for basic research in plant pathology, so that new control measures can be devised. At present, it is not known exactly what properties enable only certain specialized pathogens to cause disease, while closely related species cannot. And likewise, we do not know how plants recognize potential parasites.

Disease physiologists, studying plant pathogens and disease resistance, have been handicapped in their approaches to these problems due to the lack of good genetic systems for their use in identifying genes for virulence and constructing strains to use in biochemical studies. Plant pathogenic bacteria make excellent model systems for basic studies on host-parasite relationships since the genetics of the host and the parasite can be studied in parallel. Defining that the members of the genera Pseudomonas, Erwinia, Agrobacterium naturally exchange DNA with E. coli, and Pseudomonas aeruginosa

has given us the key to doing molecular genetics with these organisms. As a result, this is one of the most active and promising fields of plant pathology today.

But even so, there are only about a dozen laboratories in this country involved in this research, and their efforts are divided among a number of pathogens. Because manpower here is limited, and because we are working with genetically uncharacterized bacteria, it is imperative that we take advantage of the best technology available today.

Although such studies could possibly be done by classical genetics, the recombinant DNA technique offers us a usable means of genetic exchange for organisms which presently lack one. In addition, it offers the added advantage that one can now purify the genes for virulence or host specificity, study the genetic organization, and characterize their gene products. The recombinant DNA approach is faster, less equivocal, and has a greater chance for success than if the same experiments were done using classical techniques. Similar experiments have already proven valuable in the study of animal diseases.

I might add here that the problem of nodulation by nitrogen-fixing bacteria is very similar to the problem of host specificity in plant pathogens, and the same rationale applies to the field of nitrogen fixation.

In addition, studies on the genomes of plant viruses and Agrobacterium may result in the discovery of a mechanism for inserting new genes into plants. The current guidelines, established in 1976, have unnecessarily restricted cloning DNA from plants and from plant pathogenic fungi, bacteria, and viruses in several ways. First, most permissible experiments with DNA from these sources require P2 or P3 containment. This restriction appears to have been based on the unfamiliarity of NIH with plants and their parasites rather than on evidence of greater risk involving these organisms.

Second, there is a prohibition on experiments which might increase the virulence and host range of a plant pathogen. This in effect rules out complementation studies between avirulent mutants.

Third, there is a requirement that all host-vector systems be certified before you can do self-cloning experiments or reintroduce DNA which has been cloned into E. coli back into its host of origin. This latter experiment is, of course, necessary if genes for pathogenicity or nodulation are to be studied, since these properties would not be expressed in E. coli.

Moreover, this requirement for certification of hosts creates problems even for the geneticist who is not

involved in recombinant DNA research. Many very useful plasmids have been constructed in E. coli by restructuring drug resistant plasmids in vitro. At present, these plasmids cannot be transferred to other bacteria without NIH approval, even though the parent plasmids have been introduced into the species in question without any apparent danger.

The requirements for high containment levels and certification of host-vector systems have discouraged the use of cloning in work with plants, nitrogen fixation, and plant pathogens. Agricultural scientists are often obligated to divide their time between so-called basic and applied programs, and are seldom full-time geneticists. They simply do not have the time to do the extra paperwork and research needed to certify their systems. Furthermore, containment and safety equipment has rarely been needed in the plant sciences, so that compliance with the guidelines would require new purchases which might pose a hardship on young investigators.

In addition, the establishment of P2 and P3 facilities would infringe on lab space originally shared with other projects.

The proposed revisions to the guidelines solved many of these problems by exempting or lowering the containment levels required for experiments with some

of the better characterized systems. Second, they exempt self-cloning experiments. And third, they make provision for transfer of clone DNA back to its host of origin at a P1 level. The only difficulty that has come to my attention is a general concern on the part of scientists on just how much documentation and time might be required to change the classification of a particular experiment or add new organisms to the list of gene exchanges. But at least, there is a mechanism for this change, and it is very good.

In reference to the evidence upon which these revisions are based, I might say that I am in full agreement with the rationale set forth by the Workshop on Risk Assessment of Agricultural Pathogens, and feel that their findings and conclusions are based on sound principles of plant pathology. Specifically, they concluded that introduction of DNA from plant pathogens into E. coli K12 will not make it harmful to man, animals, or plants.

Moreover, it should be noted that resistance to microorganisms among plants is more common than susceptibility, and that for an epidemic to occur, you must simultaneously have large numbers of susceptible plants in one location, just the right weather conditions, and high populations of the pathogen. As a result,

plant pathogens usually have restricted host ranges and limited geographic distribution. Consequently, I believe that it should be just as safe to work with a recombinant DNA made from a plant pathogen as it is to work with the pathogens themselves.

I have spoken with a number of plant pathologists concerning the proposed revisions, and all of them are anxious to see the new guidelines implemented as soon as possible. When the proposed revisions are accepted, there will certainly be an increase in the number of plant scientists using this technique, and the benefits to agriculture could be tremendous.

I, for one, would like to use cloning to establish the relationship between plasmids and virulence in Erwinia stewartii, an important pathogen of corn.

On behalf of other plant pathologists, I urge this committee and Secretary Califano to accept the proposed revised guidelines at this time so that there will be no further delays in beginning important research on genetic improvement of crops, nitrogen fixation, and plant diseases, and in our understanding of the organisms involved.

I appreciate the opportunity to express my views today. Thank you.

MR. LIBASSI: Thank you very much.

Now, that completes the list of persons that were scheduled to speak. Is there anyone here who is to read Doug Costle's statement from EPA? If not, I would just add into the record that there is a statement [letter] from Doug Costle, the Administrator of EPA, which we will see is made a part of the record; and any other statements which we have received from persons who did not speak will also be made a part of the record and will be made available for inspection.

As a matter of information, where is the record maintained, Joe, for public inspections? Is it at NIH?

DR. PERPICH: Yes, I think it will be at NIH.

MR. LIBASSI: The full record of all the proceedings, including these proceedings and all of the materials which we will be looking at, will be available for public inspection.

Is there anyone else who had not registered earlier that would like to speak? We are pleased to make some time available for that if anyone wishes to make a comment who has not spoken.

All right; well, thank you very much, all of you, for your time. I hope we do well in our

deliberations. And we hope, in any event, to do it promptly.

Thank you all.

(Thereupon, at 2:45 p.m., the hearing was adjourned.)

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THE GRADUATE SCHOOL
UNIVERSITY OF WISCONSIN–MADISON
BASCOM HALL
MADISON, WISCONSIN 53706

September 14, 1978

MEMORANDUM:

To: General Counsel F. Peter Libassi
National Institutes of Health
2B50 Bldg. 31, Bethesda, Maryland 20014

From: Robert M. Bock, Dean, Graduate School, University of Wisconsin
Vice Chairman, Public Affairs Committee, Federated American Societies of Experimental Biology

Topic: Proposed Revised Guidelines for Recombinant DNA Research

Although scientists have been aided by the powerful new tool of recombinant DNA technology for only a few years, dramatic advances in fundamental understanding of genetics, the structure and organization of chromosomes and the detailed regulatory processes controlling replication and metabolism have already been published. This new knowledge has provided a more sound basis for modern concepts of all processes of metabolism in normal and diseased organisms. Practical applications for health care, agriculture and environmental protection have appeared more slowly, yet significant progress has been reported in producing materials of potential value to society.

The proposed Revised Guidelines for Recombinant DNA Research are reasonable, cautious and careful advances toward policies and practice which will provide society with protection from biological hazards while permitting society to benefit from the major advances in knowledge made possible by these techniques. The proposed revisions are a marked advance from the 1976 edition because expert input on infectuous diseases and pathogenicity has

been basic to the revised classifications and procedures.

It must be recognized that the proposed revisions are a needed step in an evolving process. As scientific data continues to be gathered, improved technical approaches should be considered and introduced, any problems encountered should impact our practices and the goal of safe, and efficient practices, clearly defined and well understood should remain before us.

The revised guidelines are commended for their use of good data on normal defense mechanisms and the protection of individuals who are at risk because of impairments in their normal defense processes.

While the revised guidelines recognize that Biological Safety Committees are involved in numerous important tasks other than recombinant DNA technology, there should be considerable caution in further demands on these committees which could distort their efforts out of proportion to the need to instruct, advise and assure the proper practice with known biological hazards.

The guidelines are overly presumptive in mandating a lay representative on this particular committee when a University may already have lay overview at several levels, including Boards of Regents, Public Visitors Boards, University/Community Liaison Committees, etc. In contrast to Human Subjects Committees where broad concepts of social and ethical values are necessary input, the Biological Safety Committee is an expert committee which needs breadth in expertise but which should not be diverted from its responsibility of safety.

Section IV. Roles and Responsibilities should be considered as a section to be evaluated in practice and discussed as a priority matter in subsequent revisions in the light of legislation and operational experience. Clearly, when an expert panel, such as the Recombinant DNA Advisory Committee, proposes exception to the guidelines, the Director should be authorized to approve or disapprove that exception.

Environmental Defense Fund

1525 18th Street, NW, Washington, D.C. 20036 • 202/833-1484

September 15, 1978

STATEMENT OF THE ENVIRONMENTAL DEFENSE FUND
ON THE PROPOSED REVISED NATIONAL INSTITUTES
OF HEALTH GUIDELINES FOR RECOMBINANT DNA RESEARCH
SEPTEMBER 15, 1978

Good morning. My name is Leslie Dach. I am a Science Associate with the Environmental Defense Fund (EDF). EDF is a non-profit organization with over 46,000 members. EDF undertakes legislative, judicial and administrative actions to minimize human exposure to toxic chemicals. EDF has been deeply involved in the national debate on recombinant DNA. In 1976, EDF petitioned the Department of Health, Education and Welfare to use its authority under §361 of the Public Health Services Act to regulate recombinant DNA activities. EDF submitted comments on the current NIH recombinant DNA guidelines and has testified before Congress, and the Advisory Committee to the Director of the National Institutes of Health on the issue of recombinant DNA.

EDF thanks Secretary Califano for holding this public meeting. Because of the limited time alloted to each speaker, I will only be able to touch on a small number of EDF's concerns. EDF intends to submit extensive written comments on the proposed guidelines.

Today, I would briefly like to discuss the following five aspects of the proposed revised guidelines:

1. the need to rewrite sections of the guidelines to eliminate ambiguity.

2. mechanisms for assuring adequate public participation in NIH activities mandated by the guidelines.

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3. membership of the Recombinant DNA Advisory Committee (RAC)

4. membership and responsibilities of the Institutional Biosafety Committees (IBCs).

5. confidentiality

EDF is concerned that the poor quality of the drafting of the guidelines will result in confusion and compliance failures. As presently written, instructions for persons conducting recombinant DNA activities are spread throughout the proposed guidelines themselves, the Director's decision document, the Environmental Impact Assessment (EIA) and appendices to these documents. Often, these documents contradict each other. But only the guidelines will have the indisputable force of law. Moreover, the guidelines are sometimes so vague that their intent is unclear, and problems are sure to arise.

The section of the Federal Register package dealing with certification of host-vector systems exemplifies these problems. The guidelines state that certain new host-vector systems "may not be used unless they have been certified by NIH." But there is no indication of what office within NIH supplies this certification. The person seeking certification does not know if he or she is free to use the host-vector system after approval by the Recombinant DNA Advisory Committee or if they must wait for approval of the NIH Director. Just this sort of ambiguity was cited by the University of California at San Francisco to explain their violation of the existing guidelines.

Another example of poor drafting is in the section of the guidelines dealing with exceptions from prohibited experiments. The Director's decision document indicates that the rationale for allowing exceptions is to provide for experiments for which there are compelling social or scientific reasons (43 Fed. Reg. 33048). Yet the guidelines

themselves (43 Fed. Reg. 33070) merely indicate that weight will be given in the decision making process "both to scientific and social benefits and to potential risks." Clearly, the standard for excepting experiments is different in the two documents.

When differing interpretations of the same issue are given in different sections of the Federal Register package, it is impossible for EDF or a person conducting a recombinant DNA activity to ascertain which is the correct one. In addition, it is unrealistic to assume that the reader will scour all the documents in the Federal Register. Most important, the EIA and the Director's decision document do not have the indisputable force of law. EDF therefore maintains that all information necessary for compliance be included in the guidelines themselves. Finally, ambiguties such as the one described within the guidelines should be clarified.

The second area of concern I will discuss today is the failure of the guidelines to specify procedures for public notification and public comment. The guidelines often indicate that a decision will be made "after appropriate notice and opportunity for public comment." (43 Fed. Reg. 33070). No clarification of this is given. For example, the section of the guidelines dealing with certification of new host-vector systems makes no mention of procedures for public notification or public comment. (Interestingly, the Director's decision document states (43 Red. Reg. 33057), "I agree that prior notification to the public should in the Federal Register be given when the RAC considers applications for certification.")

The procedures for public notification and comment must be described, in detail, in the guidelines. Failing this, the public

will have no assurance that opportunity for public comment will be provided. If pressure for a quick decision is strong or NIH wishes to avoid public scrutiny, the guidelines enable it to make decisions in secret. In addition, valuable resources are likely to be wasted fighting out the mechanism of "appropriate opportunity for public comment," each time the opportunity is given

As an example of how public participation mechanisms should be constructed, EDF proposes the following mechanism for decisions concerning exceptions from prohibited experiments.

Within 10 days of receipt of an application for an exception from a class of prohibited experiments, NIH should publish in the Federal Register notice of the receipt, details of where the material submitted in support of the exception can be obtained and the closing date of the public comment period. At a minimum, the comment period should be 45 calendar days. Final notice of agency action should also be published in the Federal Register. All material submitted to NIH should be available to the public.

Our third area of concern is the membership of RAC. The guidelines (43 Fed. Reg. 33086 and 33087) describe the functions of RAC. They include recommending revisions in the guidelines, exceptions from prohibited experiments and exemptions from the guidelines. These decisions involve weighing both social and scientific risks and benefits. This is especially true for allowing exceptions from classes of prohibited experiments. Such decisions are clearly not purely scientific ones. As such, RAC must include non-scientist members who adequately represent the interests of the general public. The guidelines do not provide for this. They do not contain any provisions for selecting RAC members. (Again, the Director's decision

document mentions this issue. It indicates that two non-scientists are currently RAC members and that more public members may be added.)

Our written comments will provide more details on this issue. Requirements similar to the ones I have outlined are contained in HEW's proposed regulations for the governing bodies of Health Systems Agencies (43 Fed. Reg. 22858).

EDF maintains that at least one-third of the RAC be composed of individuals who are not engaged in biomedical research and who can reasonably be expected to represent the interests of the general public. Such individuals would include representatives of labor, public interest groups and elected or appointed public health officials. A subcommittee composed of a majority of RAC members who represent the interests of the general public should be given authority to make recommendations to the Director of NIH concerning exceptions to prohibited experiments and exemptions from the guidelines.

I will discuss our final two areas of concern, confidentiality and the membership and responsibilities of the Institutional Biosafety Committees simultaneously. IBCs have primary responsibility for insuring compliance with the guidelines.

I do not have time to describe the membership and responsibilities of IBCs as outlined in the proposed guidelines. I will therefore proceed immediately to a description of the changes EDF feels are necessary.

One-third of the membership of each IBC should be composed of individuals who have not been affiliated with the institution for at least a year prior to their service on the IBC. At least one of these individuals should be a non-doctoral person from a laboratory technical staff. This person should be elected by the institution's technical

staff. At least one person should represent the health department of the local government. This person should be selected by the health department. The remainder of the non-affiliated members should be persons who may be reasonably expected to represent the interests of the community.

The membership ratios EDF suggests are necessary to insure that IBCs will satisfactorily perform their oversight and regulatory roles. It is well known from studies of medical licensing and disciplinary boards and from the events surrounding the violations of the recombinant DNA guidelines at Harvard Medical School and University of California at San Francisco that peer review does not provide adequate public protection. The proposed guidelines' requirement for one non-facility member does not address this issue. There is no provision that this individual represent the public interest. The person could very well be a recombinant DNA scientist from a neighboring institution.

Turning to confidentiality, EDF maintains that all IBC meetings should be announced and open to the public. All MUAs and project registrations from institutions that must comply with the guidelines should also be available to the public. EDF's reading of applicable statutes (5 U.S.C. §552 and 18 U.S.C. §1905) indicates that such information, submitted to IBCs or NIH, is not exempt from the provisions of the Freedom of Information Act (5 U.S.C. §552). In light of their legal authority under the guidelines, IBCs are agencies within the meaning of 5 U.S.C. §552. 5 U.S.C. §552 gives NIH the discretion to withold trade secrets from the public. 18 U.S.C. §1905 provides a cirminal penalty for violation of an explicit prohibition against revealing trade secrets or confidential statistical information. No

such prohibtion exists here. Moreover, the courts have held that the research designs and protocols of non-commercial scientists are not trade secrets and therefore must be revealed to the public under 5 U.S.C. §552. Washington Research Project v. Department of Health Education and Welfare 504 F.2d 238(1974). This decision applies to all recombinant DNA activities regardless of whether the investigator plans to seek a patent on his research. In addition none of the information EDF maintains should be available to the public meets the test for confidential commercial information contained in National Parks and Conservation Association v. Morton(498 F.2d 765(1974)).

EDF maintains that no changes in ongoing recombinant DNA projects subject to the guidelines should be allowed without NIH approval. The error rate of IBC's has been variously estimated at 4-15% by NIH's Office of Recombinant DNA Activities (ORDA). The turn around time for ORDA review of an IBC assessment of containment requirements is 4-5 days. For these two reasons, EDF maintains that no changes should be allowed without ORDA approval. To speed up the turn around time, EDF suggests that ORDA be given additional staff. There are presently only two people reviewing IBC assessments of containment requirements.

Statement by June E. Osborn, M. D. Professor of Medical Microbiology and Pediatrics, University of Wisconsin-Madison

September 15, 1978

My purpose in making a comment concerning the revised guidelines for recombinant DNA research is to support the general direction of proposed changes, rather than to comment on specific provisions. I am a pediatrician who specializes in infectious diseases and also a microbiologist whose primary focus has been mechanisms of pathogenesis of microorganisms. As such I have been concerned from the outset of the recombinant DNA debate with the relative lack of recourse to the substantial fund of knowledge concerning known pathogenetic mechanisms of genuinely virulent organisms. The inference has sometimes been that pathogenetic mechanisms of microbes are generally unknown and mysterious and that, once pathogenic, organisms are uniformly so in an all-or-none fashion. As I read the revised guidelines I was therefore pleased to note that the proposed changes move substantially toward a thoroughly rational, cautious approach to facilitating advances in research under conditions of sensible containment.

Perhaps some consideration of known facts about pathogens will amplify my first point: that the revised guidelines are sensible in their emphasis on the human host who would be the initial biologic target of an inadvertently released vector. A healthy adult who is not undergoing antimicrobial or immunosuppressive therapy is usually an effective barrier even against pathogenic microorganisms that have been millenia in the making. For instance the meningococcus - which can produce meningitis and/or overwhelming sepsis - is far more commonly carried by a substantial fraction of the population as a harmless component of the throat flora in the winter months. More pertinently, "virulent" E. coli organisms - not even the weakened strains about which much debate has centered - are poor pathogens at best; and while certain bacterial products made by some strains are thought to augment their potential invasiveness, the vast majority of instances of serious E. coli disease occur in infants or in hosts with immunologic or anatomic predisposition.

My second point is complementary to the first: even the most virulent of microorganisms has a "dosage" threshold below which its mechanism of pathogenesis fails. When persons are bitten by a demonstrably rabid wolf, less than half proceed to get rabies; and the presumed reason for the others' failure to become ill is a dosage effect. It has been shown experimentally that 20,000,000 virulent group A streptococci are required in order to establish a pharyngitis in human volunteers; and a million coagulase positive staphylococci can be injected into healthy human skin without causing disease (whereas the presence of an inert foreign body such as a suture in that skin suddenly allows 100 staph to establish purulent infection - again emphasizing the importance of the host's role in successful pathogenesis by microorganisms).

Insofar as mechanisms of pathogenesis are concerned, much again is known about the established pathogens of man. Group A streptococci

make M protein which conveys an anti-phagocytic resistance to the bearer. Pneumococci make a capsular polysaccharide which serves a similar function. Diphtheria bacilli are entirely innocuous unless they themselves are infested with a lysogenic phage, and even then proper iron concentrations and other environmental conditions are necessary before toxin production can proceed....and so forth. It is interesting to note that even in the case of drug resistance where much of our new infectious disease problems lie, the multiply drug-resistant tubercle bacillus has reduced virulence as a correlative property.

I have conducted this brief exercise in medical microbiology to establish several points:

1) that emphasis on the human host working in the environment of potentially "new" microorganisms is appropriate;

2) that dosage is an important element in known pathogenetic microbial disease and so sensible efforts at containment - with particular attention paid when microorganisms are at high concentration - can be imposed with a degree of confidence;

3) that known, highly virulent pathogens are in general the product of marvelous evolutionary adaptation which allows them to co-exist in the so-called "carrier state" far more often than to cause disease in their human host. (In this context, the proposal to deal with DNA from viral pathogens at a level of containment no higher than that appropriate to the parent virus seems eminently sensible).

The broader point I would like to make is that biology in general, and infectious disease microbiology in particular, submit to the same rational analysis as do other arenas of science; and while unknowns remain, much hard data and experience can be brought to bear on such discussions as the present consideration of recombinant DNA research.

I therefore want to voice my support for the revision of the guidelines currently proposed.

Thank you.

June E. Osborn M.D.

June E. Osborn, M. D.
Professor of Medical Microbiology
and Pediatrics
Associate Dean of the Graduate School
(Biological Sciences)

STATEMENT

BY

HARLYN O. HALVORSON, PH.D.

PAST PRESIDENT

AMERICAN SOCIETY FOR MICROBIOLOGY

BEFORE THE

HEALTH, EDUCATION AND WELFARE HEARING

ON

PROPOSED REVISIONS OF THE GUIDELINES

FOR RECOMBINANT DNA RESEARCH

SEPTEMBER 15, 1978

Mr. Chairman, Members of the Committee:

On behalf of the American Society for Microbiology (ASM) I want to express our appreciation for the opportunity to testify before you on the proposed revised guidelines for recombinant DNA research as published in the Federal Register on Friday, July 28, 1978. For a number of years ASM has had a long and a continuing interest in recombinant DNA research, regulations, training and legislation. A number of Committees have been following this field. These include: (1) An Ad Hoc Committee under Dr. H. Ginsberg, which carried out an independent review of the initial guidelines and participated in discussion on the present guidelines; (2) Public Affairs Committee, in collaboration with a number of other scientific societies, has developed consensus positions concerning regulation of this research; and (3) An ASM Working Panel concerned with the training in microbial techniques for conducting recombinant DNA research. I addition, we have broadly solicited the views of our members. In the brief time available today I would like to restrict my remarks to five main issues concerning guidelines and submit, with your permission, for the record some specific recommendations for future review by the Recombinant DNA Advisory Committee. Portions of my statement reflect the consensus developed with other scientific societies in the last several years.

(1) Development of the Guidelines

ASM, in coalition with other scientific societies has testified before Congressional hearings that the NIH guidelines, as periodically modified by new information, are appropriate for determining national policies to govern research on recombinant DNA molecules.

The experience of the past few years justifies this approach. We applaud the excellent job that the Director, the staff at NIH and the Recombinant DNA Advisory Committee has done in developing the new guidelines. We further endorse the addition of representatives of critical disciplines in epidemiology, infectious diseases, medical microbiology and virology as advisors. Their expertise and workshops such as the Falmouth meeting, the ASOT meeting and the workshop on Risk Assessment of Agricultural Pathogens in Washington provide essential, valuable input in evaluating the available scientific information. We believe that this approach is sound and increases the confidence and quality of decision making. New hosts and vectors in recombinant DNA research are to be expected, and the procedures to evaluate and assign appropriate levels to each have been developed by NIH.

(2) Changes in Containment Levels

During the last two years there have been dramatic contributions from recombinant DNA research to both fundamental concepts in biology and to applications in biomedicine. Concern over freedom of research and protection of the public, in such a rapidly changing field are, and will continue to be, characteristic of this field. We support the approach by NIH to continually review the risk asssessment data of host-vector systems in DNA recombinant research to provide conservative guidelines. The lowering of containment levels for recombinant DNA research based on viral vectors, following detailed evaluation of experience with animal viruses (ESCO meeting and Ginsberg Report) represent the type of public responsibility in evaluating risk experience, which should serve as a model for other host-vector systems. The resulting reductions in containment levels, in our opinion, are justified and based on sound principals of pathogenicity and epidemiology. We recommend that in the continuing process of risk assessment that the appropriate experts, as Committee

members or Ad Hoc Committees, be employed and that their evaluations continue to be exposed to public scrutiny. The use of workshops, special studies and open, publicized meetings of the Advisory Committee are sound and appropriate procedures to reevaluate containment levels of host-vector systems.

(3) Responsibilities of Institutional Biosafety Committees (IBC)

In testimony last year before the Kennedy Subcommittee hearing on DNA recombinant research, we suggested that the institutional biosafety committees should have a leading role in assessing individual laboratories as to the adequacy of safety procedures, the appropriate levels of physical containment and biological containment, the provision of educational materials and the review of experimental design. We support these developments in the revised guidelines and reiterate that the local groups are more knowledgeable of the strengths and weaknesses of any scientific colleague than would be possible with governmental review agencies. This procedure has a proven history in protecting human subjects in medical centers.

Increasing authority to the IBC carries with it the responsibility of assuring that this committee has the relevant scientific expertise and public (non-institutional) representation. We suggest that the NIH Advisory Committee may want to consider in its further development of policies, recommendations on the composition of the IBC to ensure that it is capable of fulfilling its responsibility. As we pointed out in the Stevenson hearing the above recommendation carries with it an obligation of NIH to bear some financial costs for appropriately transferring Federal responsibility to IBC's.

(4) Authority of the Director of NIH to Make Exceptions

We are firmly convinced that it is essential to continue to provide authority of the Director of NIH, with appropriate study review, to make exceptions to the guidelines. First, experience has shown that this authority is exercised with care and only after careful review. Second, since the development

of the initial guidelines one cannot anticipate in such a rapidly moving field, all the advances, opportunities and new information on natural gene transfers or of risk assessments. For example, it is not unlikely that B. pumulis and B. subtilis may naturally exchange genetic information. If this could be demonstrated, such recombinant DNA experiments should be permitted. Thirdly, there are a series of experiments which should be conducted under highly controlled (P4) conditions. Recombinant research with class 3 etiological agents are not permitted in spite of the need to explain basic mechanisms of pathogenicity with these agents and, in spite of the existence of a national P4 facility. Our greatest need is for good risk analysis, particularly with class 3 organisms, in which knowledge of genetic systems is scanty and in which our own need to develop defensive mechanisms is the greatest. The need, for example, to conduct the risk assessments of Dr. W. Rowe with polyoma virus with wild type E. coli is essential in developing national policy. Thus, we believe it is important that the Director have such authority, following proper review and the availability of an appropriate (P4) facility, to permit such type of experiments.

(5) Roles and Responsibilities

Our last, but not least, issue concerns the assignment of responsibility. For the past two years we have supported the view that substantial responsibility be transferred to the IBC. We approve of the recommendations in Section IV of the guidelines to implement this goal. For research in the public sector we are convinced that license revocation and withholding of Federal funds are both sufficient and effective restraints to effect compliance with the guidelines. Research in the private sector is not covered by the guidelines and can only be corrected by legislation. We note that PMA, and individual company representatives, have committed their organizations to volunteer complicance to Federal guidelines.

While supporting the present proposed guidelines, we are concerned that NIH retain surveillance over local biohazard committees. It is important that NIH have the authority to assure uniform, national standards of compliance to these guidelines. In the absence of overriding Federal legislation, the responsibilities defined in the July 28, 1978 guidelines represent an acceptable interim.

STATEMENT OF HON. RICHARD L. OTTINGER
ON RECOMBINANT DNA RESEARCH REGULATION
September 15, 1978

Mr. Chairman, members of the panel, I appreciate the opportunity to appear before you this morning.

I would just like to make a few brief remarks this morning about the urgency with which I am convinced HEW must act to regulate recombinant DNA research.

As the first Member of Congress to have introduced legislation on this matter nearly two years ago, I have watched with escalating concern the increase in commitments, particularly in the commercial sector, to recombinant DNA research.

Quite simply, the whole matter is rapidly getting out of control, and it is at this juncture appropriate for HEW to take the reins and protect the public from any further loss of control until Congress acts.

The failure of the Congress to act is one which deeply troubles me, and I am personally very disappointed. But that failure is not one upon which HEW should now base any excuses for inaction. Rather, it is directly because Congress has not acted and cannot act during this session that I come before you today to urge your action.

The failure of the Congress resulted from some of the most vigorous and, in many instances, distasteful, lobbying I have ever seen on any issue. When the scientific establishment gangs up on Congress, touting its expertise as the only thing going and claiming to be capable itself of protecting the public, it seems clear that Congress is hard-pressed to resist. Those sorts of assertions must now be resisted by HEW.

Recombinant DNA research has the potential for bringing us some of the greatest horror stories since we dropped the atomic bomb in Japan. The recent transport of smallpox from England to the United States is illustrative of the kind of problem we might face with DNA research. We were told a year ago by the World Health Organizaiton (WHO) that smallpox had been eradicated and was only a

concern for historians. It is now clear such optimism was premature. While smallpox may have been confined to labs, mostly for archival purposes, the threat to public health was not entirely eliminated.

The virus in England escaped through a "faulty filter," and contaminated workers in and around a laboratory at Birmingham University. A medical photographer fell victim to this virus and died. The director of the lab committed suicide. The threat from this outbreak even spread to the U.S. when an individual exposed in England flew to North Dakota.

This episode with smallpox parallels and highlights several concerns about research in the area of genetic manipulation:

1.) Labs cannot provide foolproof containment of dangerous organisms;

2.) Biohazard outbreak, unlike any other type of threat, can rapidly spread to virtually any neighborhood on earth;

3.) The more over-optimistic the picture painted by the scientific community, the more vulnerable the public is to health disasters, especially from unprecedented, genetically-hybrid forms, against which nature may have evolved no immune mechanisms.

I realize that stringent safeguards on this type of research may be expensive and/or have an inhibiting effect on the progress of research. But we treat the threats casually, at our own peril.

HEW must now act, and I would urge that you do so under Section 361 of the Public Health Service Act. It may not be the perfect instrument, but at least it provides some authority for action. I do wish I could assure you that the Congress would quickly provide you more precise authority, but I cannot. Even if we were to act early next year, and that's doubtful, it would take an additional year to prepare regulations.

We cannot afford to wait any longer. Imperfect as the world is and as Section 361 is, waiting is going to make matters much worse.

THE COMMITTEE ON GENETIC EXPERIMENTATION
A SCIENTIFIC COMMITTEE OF THE INTERNATIONAL COUNCIL OF SCIENTIFIC UNIONS

First Report to COGENE from The Working Group on Risk Assessment

A. M. SKALKA (USA) Convenor
G. BERNARDI (France)
V. SGARAMELLA (Italy)

July 1978

A Description of COGENE

The parent body of the Committee on Genetic Experimentation (COGENE) is the International Council of Scientific Unions (ICSU), an international non-governmental scientific organization of 18 autonomous international Scientific Unions and more than 60 National Members, i.e. academies of science, research councils or similar scientific institutions.

COGENE was created by decision of the 16th General Assembly of ICSU and came into being in 1977. It is a Scientific Committee, one of a type formed by ICSU whenever a task is defined that is of major interest to several unions and the program is of a long-term nature. COGENE is supported by seven member unions — Pure and Applied Chemistry, Biological Sciences, Biochemistry, Pure and Applied Biophysics, Nutritional Sciences, Pharmacology and the Immunological Societies — and includes a number of scientists prominent in the field of recombinant DNA research, which is currently the major focus of interest of COGENE and the reason why the Committee came into being.

Membership

A.A. Bayev (U.S.S.R.)
G. Bernardi (France)
S.N. Cohen (U.S.A.)
A.F. Langlykke (U.S.A.)
K. Murray (U.K.)
N. Notani (India)
R. Riley (U.K.)
A.M. Skalka (U.S.A.)
C. Steinberg (Switzerland)
J. Tooze, Secretary (BRD)
I. Watanabe (Japan)
W.J. Whelan, Chairman (U.S.A.)
E. Wollman (France)

Observers have been appointed by FAO, ICRO, UNEP, UNESCO and WHO. Twenty-one nations have appointed National Correspondents.

Purposes and Objectives

The terms of reference of COGENE include the following purposes and objectives:

COGENE is a Scientific Committee of ICSU, established to serve as a nongovernmental, interdisciplinary and international council of scientists and as a source of advice for the benefit of governments, inter-governmental agencies, scientific groups, and individuals, concerning recombinant DNA activities.

Among its purposes shall be:

a) to review, elvaluate and make available information on the practical and scientific benefits, safeguards, containment facilities and other technical matters,

b) to consider environmental, health-related and other consequences of any disposal of biological agents constructed by recombinant DNA techniques,

c) to foster opportunities for training and international exchange, and

d) to provide a forum through which interested national, regional and other international bodies may communicate.

COGENE shall also consider, if necessary, other related activities which may give rise to public concern.

Current Activities

COGENE currently has three Working Groups active in the areas of:

a) Guidelines for Research on Recombinant DNA. The Convenor is S.N. Cohen (U.S.A.). The Group will make its first report in September 1978.

b) Risk Assessment Experiments. The Convenor is A.M. Skalka (U.S.A.). This is the Group's first report.

c) Benefits and Applications of Recombinant DNA. The Convenor is W.J. Whelan (U.S.A.).

COGENE and the Royal Society (Great Britain) will convene an international conference on recombinant DNA at Wye College (University of London) Kent, U.K. during 1-4 April 1979.

SUMMARY

The Working Group has been charged with the task of gathering information related to assessment of risks associated with recombinant DNA research. The information in this report was obtained by observation and participation at a number of meetings and hearings, by survey of the literature and by direct inquiry to national and international organizations, and individual scientists.

Our analyses indicate that the concerns regarding recombinant DNA research can be summarized as follows:

1. Organisms carrying recombinant DNA may spread in the natural environment and disrupt existing ecological equilibria.
2. These organisms might produce some toxic or noxious substance, or otherwise cause disease.
3. By exploiting this technology, scientists may be crossing some hypothetical barrier to DNA exchange between eukaryotes and prokaryotes and thus affect pathogenicity or dispersion of pathological agents.

Reports from the Falmouth Meeting (section IV) and COGENE-sponsored analyses of *E. coli* K-12 systems (section VI) show that many relevant experiments have already been conducted by scientists in such closely related fields as epidemiology and infectious diseases. Their observations that *E. coli* K-12 has a limited prospect of survival and their consensus that this bacterium cannot be converted into an epidemic pathogen by laboratory manipulations with DNA inserts, do much to satisfy the first concern mentioned above. In addition (section VII), long-term monitoring of laboratory workers who routinely handled K-12 organisms carrying transmission-proficient plasmids showed no bowel colonization despite the fact that the work was carried out without any special precautions. If the organisms which carry recombinant DNA cannot spread in the natural environment, then clearly the other concerns are also diminished. The conclusion of a NIH/EMBO Virology Workshop (section V) was that recombinant organisms carrying viral inserts cannot be any more hazardous than the viruses themselves, and in some instances may provide an opportunity to work more safely with virulent agents.

As will be seen in the report, important information on the nature and possible consequences of the manipulations used in recombinant DNA technology comes from experiments in a variety of fields. For example, attempts to understand the biological role of restriction enzymes have revealed that prokaryotic and eukaryotic DNAs can recombine *in vivo*. Other studies, including those with *Agrobacterium tumefaciens* and plant cells, also show that in some cases there is no natural barrier to exchange and expression of genes across the hypothetical prokaryotic-eukaryotic barrier. On the other hand, studies of animal virus genomes and eukaryotic genes for differentiated functions have revealed previously unsuspected possible barriers to their expression in

prokaryotic backgrounds. It is clear that further studies of the molecular genetics, pathogenicity, ecology and other properties of organisms will continue to provide information relevant to the assessment of risk and that this source is no less important than specifically targeted experiments.

Replies to our Questionnaire (sections I and II) indicate that there are several projects currently underway directed specifically towards risk assessment. These include the two separate polyoma virus experiments currently sponsored by EMBO and by NIH and several NIH contracts aimed at testing and verification of EK2 and EK3 systems. Preliminary results, as well as conclusions from the NIH-EMBO Virology Workshop indicate that these studies are unlikely to reveal unknown hazards. These and other experiments which are aimed at elucidating various aspects of the ecology and natural history of microorganisms should provide useful information and will be important in the development of host-vector systems other than those based on *E. coli* K-12.

In summary, our analyses have revealed no scientific findings to justify any of the three concerns listed above; no risk unique to recombinant DNA research has been identified. Available evidence indicates that recombinations of the type made possible by this new technology can occur in Nature. Evaluation of *E. coli* K-12 shows that this bacterium is essentially harmless and that insertions of segments of foreign DNA into its genome cannot alter this property. With few exceptions, it seems likely that the same will prove true of other host bacteria. These conclusions cannot be ignored if the guidelines governing recombinant DNA research are to remain rational and useful.

Part I of the following report contains a detailed summary of information we have gathered and a selected bibliography. Part II includes source materials, documents received in reply to our questionnaire and the texts of reports which may not be readily available.

[A full copy of this report may be obtained from

Dr. W.J. Whelan
P.O. Box 016129
Miami, Florida 33101
U.S.A.]

Summary of Statement Before the Department of Health, Education, and Welfare Review Committee on the NIH Proposed Revised Guidelines for Recombinant DNA Research

By

Dr. Robert M. Faust
Plant Protection Institute
Science and Education Administration
United States Department of Agriculture
Beltsville, Maryland 20705

The USDA is generally satisfied with the considerations that the NIH has incorporated into the revised recombinant DNA guidelines dealing with the concerns of agricultural scientists regarding the easing of restrictions for recombinant DNA research with plants, non-private vertebrates and invertebrates. We also note with satisfaction the NIH attempt to meet the concerns of agricultural scientists regarding release of recombinant DNA-containing organisms into the environment. The USDA wishes to reemphasize its desire to be deeply involved in this process and is concerned with the details of the mechanism of waiver proposed.

We are confident that institutional biosafety committees can be relied upon for authoritative and proper implementation of the Guidelines provided those committees are required to be organized and established according to the recommendations of the NIH.

A few questions have arisen concerning certain interpretations of the revised guidelines that relate to the specific scientific and research containment procedures. The possibility of using recombinant DNA procedures for the development or improvement of safe entomopathogenic strains of bacteria for insect management has been suggested. The interpretation, however, of the levels of biological and physical containment required by the revised Guidelines is a rather bothersome

issue, largely owing to the lack of a concise meaning for pathogen and polypeptide toxin mentioned throughout the Guidelines. We also question the necessity for EPA registration of an entomopathogenic organism in lieu of simply meeting the criteria of EPA for a temporary exemption from a requirement of tolerance in the environment. Lastly, we would suggest that the NIH clarify the meaning of a P1 insect proof greenhouse in regards to cloning genes in plants. We believe it is virtually impossible to have a P1 facility that is insect proof and still remain classified as P1.

Statement Before the Department of Health, Education, and Welfare Review Committee on the NIH Proposed Revised Guidelines for Recombinant DNA Research

By

Dr. Robert M. Faust
Plant Protection Institute
Science and Education Administration
United States Department of Agriculture
Beltsville, Maryland 20705

September 15, 1978

In October of 1977 the Agricultural Research Policy Advisory Committee's (ARPAC) subcommittee on agricultural recombinant DNA research was established to concern itself with matters relating to guidelines for recombinant DNA research and any regulatory processes that might develop. It also was assigned the responsibility for developing recommendations and possible model procedures indicating how agriculturally related sciences and their sponsoring organizations should be moving forward to conduct recombinant DNA research, identify and share beneficial findings and foster safe application of such findings. The committee responded to the USDA's "Notice Regarding Research Involving Recombinant DNA Molecules", which purpose was to state USDA policy with respect to the administration and conduct of research involving recombinant DNA. We recommended that the Joint Council on Food and Agricultural Sciences develop standardized procedures for extramural and intramural recombinant DNA research to assure that the same guidelines are being followed and honored, that the "Notice Regarding Research Involving Recombinant DNA Molecules" developed by the USDA Recombinant DNA Committee be accepted, that wherever feasible, scientists working on recombinant DNA should be governed by a local biosafety committee, regardless of the source of funds, and that the conditions for performing recombinant DNA research as published in the Federal Register, Vol. 41, No. 131, dated July 7, 1976, be

adopted as USDA policy and adhered to by researchers for which USDA funds are used either intramurally or extramurally, or through grants, contracts, and cooperative agreements.

Although the committee recommended the adoption of the NIH guidelines as a part of USDA policy, members of the committee did express their concerns with the extremely restrictive nature of the 1976 guidelines that particularly impeded the application of recombinant DNA technology in agriculture for such projects as genetic improvement of food and fiber crops and the development of more useful and reliable biological insect control agents such as the baculoviruses and entomopathogenic bacteria in lieu of certain hazardous chemical insecticides. We are generally satisfied with the considerations that the NIH has given and incorporated into the revised guidelines, especially for those major suggestions for revision that were made to NIH as a result of the Airlie House meeting and the workshop on Risk Assessment of Agricultural Pathogens. We further note with satisfaction NIH's attempt to meet the concerns of agricultural scientists regarding the easing of restrictions for recombinant DNA research with plants, non-primate vertebrates and invertebrates and regarding the release of recombinant DNA-containing organisms into the environment. Although the NIH has incorporated a statement to the effect that the prohibition of deliberate release into the environment of recombinant DNA-containing organisms can be waived if all of the requirements for a waiver are met, we would like to reemphasize it is obligatory that the U. S. Department of Agriculture be deeply involved in this process. Our main concern with this item resides in the mechanism of waiver, the definitive requirements for a waiver, and the latitude that the waiver allows for release. We would encourage the NIH to draw upon their resources, such as the USDA, OSHA, and the Environmental Protection Agency, in order to furnish researchers more definitive guidelines for the waiver.

There has been some suggestions made that the Institutional Biosafety Committees are self-serving, ineffective, and in reality are only researchers regulating themselves. As chairman of the Beltsville Agricultural Research Center's Biosafety Committee I take exception to this suggestion. The membership of our committee was purposely made diverse and includes (1) individuals from a number of scientific disciplines, (2) individuals who are knowledgeable about laboratory safety and engineering principles, and (3) several laboratory technical staff. Our first recombinant DNA project submitted for certification to the committee was in fact returned twice for further elaboration before complete approval by the membership was given. Committee members recognize that such research may involve biohazards and are mindful of the public concern on recombinant DNA. Further, it is well recognized that it is essential all research involving the use of recombinant DNA molecules be conducted in a responsible manner, adhering to safety precautions and conditions designed to protect laboratory workers, the general public, and our environment. Earlier this year I had the opportunity to attend a Biosafety Committee meeting at the Scripps Clinic and Research Foundation in La Jolla, California. The Scripps biosafety committee had a similar profile and were extremely effective and non-partial in their deliberations. I am certain without any reservations that institutional biosafety committees can be relied upon for authoritative and proper implementation of the guidelines, provided those committees are required to be organized and established according to the current recommendations of the NIH.

Lastly, some questions have arisen at the Agricultural Research Center concerning certain interpretations of the revised guidelines that relate to the specific scientific and research containment procedures that the proposed revisions require. The possibility of using recombinant DNA procedures for the

development or improvement of entomopathogenic strains of bacteria for insect management has been considered by myself and I have begun some of the basic research necessary to facilitate the use of bacteria towards this end. Envisaged are possible applications of in vitro gene splicing and recombinant DNA cloning to (1) expand the insect pest host spectrum of existing insect pathogens, (2) develop more potent strains of pest insect pathogens, (3) improve the physiological tolerance and epidemiological properties of these bacteria, and (4) facilitate the in vitro commercial production of the more fastidious insect pathogens by expanding the range of substrates upon which they can grow. Two of the present organisms with which I am working, Bacillus popilliae, the Japanese beetle pathogen, and B. thuringiensis, a pathogen of pest caterpillar larvae, both enjoy EPA registration and exemption from tolerance in the environment.

Back in October of 1977 a copy of my proposed recombinant DNA program was forwarded to the NIH office of Recombinant DNA Activities for comment and clarification of certain aspects of the 1976 NIH guidelines dealing with shotgun experiments in procaryotes. Apparently, the NIH Recombinant DNA Advisory Committee was unable to come to a definitive decision on the proper containment levels for in April, 1978 I received a letter from William Gartland, Director, Office of Recombinant DNA Activities (ORDA) suggesting that I submit a draft statement for consideration by ORDA on the containment levels for recombinant DNA research with entomopathogenic bacteria that have EPA registration. On April 24, 1978 I submitted such a statement as requested.

Although the proposed revised guidelines will simplify the problem of interpretation there is still left a rather bothersome issue that may also be found in other sections of the guidelines. Under section III-B (Experiments with Other Prokaryotic Host-Vectors) host-vector systems which have been approved as

HVI systems may be used under P2 containment conditions for shotgun experiments with phages, plasmids, and DNA from nonpathogenic prokaryotes which do not produce polypeptide toxins. Therein is the quandary! Both of the proposed organisms for recombinant DNA research are pathogenic, but only to target insects, and one of them, B. thuringiensis produces a polypeptide toxin which is the basis of its pathogenicity. The toxin, however, is only specific for certain insects and has been deomonstrated ineffective against other life forms - including man. I would respectfully request that the NIH define more concisely the nature of the pathogenicity and the types of polypeptide toxins meant in the revised guidelines. That is to say, pathogenic and/or toxic to what life forms? Further, the investigator is hard pressed to analyze the biological containment requirements for such experiments. Can an organism that grows in an insect or is found as a common soil organism, but only affects certain insects, be developed for pest control use and be considered an HV-1 system for shotgun experiments using DNA from entomopathogenic bacteria. The revised guidelines apparently do not adequately address such types of bacterial recombinant DNA experiments. We further would ask the NIH to consider that the entomopathogenic bacteria or the baculoviruses be only required to meet the criteria of EPA for a temporary exemption from a requirement of tolerance which verifies that the organism has been rigorously tested for safety to mammals and other non-target organisms in the environment rather than have EPA registration for a specific containment level. Registration of the organism is granted only afterwards provided the organism is shown to be efficacious.

In section III-C-3 (Plant Viral Host-Vector Systems) dealing with DNA plant viruses serving as vectors for cloning genes in plants, we question the statement that "the plants should be grown under P1 conditions - that is in

either a limited access greenhouse or plant growth cabinet which is insect proof,"... Rather than insect proof perhaps the NIH means insect restrictive since insect proofing infers a facility greater than P1 as recommended. The statement appears to be contradictory.

Thank you.

State of New Jersey
DEPARTMENT OF HEALTH
DIVISION OF COMMUNITY HEALTH SERVICES
CONSUMER HEALTH SERVICES
1911 PRINCETON AVENUE
TRENTON, N.J. 08648

JOANNE E. FINLEY, M.D., M.P.H.
COMMISSIONER

September 14, 1978

Mr. F. Peter Libassi
General Counsel
Department of Health, Education and Welfare
National Institute of Health
Building No. 31, Room 2B50
Bethesda, MD 20014

Dear Mr. Libassi:

On behalf of the Department of Health and the Public Health Council of the State of New Jersey, we are in full support of the efforts of the National Institutes of Health, the scientific community and public interest groups which have enabled the development of Guidelines on Recombinant DNA Research.

In the State of New Jersey we are concerned about the conduct of research at all institutions which have on-going projects or are planning projects involving Recombinant DNA. In particular, we are concerned about research at those institutions which do not receive NIH funds and are not subject to the NIH Guidelines.

Therefore, we strongly urge you to retain in the final version, Sections IV-C-2, IV-C-3, and IV-C-4 of the NIH Revised Guidelines as published in the Federal Register, Vol. 43, No. 146, Friday, July 28, 1978. These sections are titled "Voluntary Registration and Certification", "Disclosure of Information", and "Patentable Materials".

In essence, by retaining these sections, any institution which is not covered by the Guidelines will be permitted to register their Recombinant DNA Research Projects with NIH, and can request certification of proposed host-vector systems by NIH. The registrants will in turn be required to abide by the physical and biological containment standards of the NIH Guidelines.

As you know, review of project proposals and certification of host-vector systems requires enormous resources both in terms of scientific personnel and finances. Thus, it would place a heavy burden on state governments if NIH decides not to retain the above cited sections of the NIH revised Guidelines.

Retention of the section which will permit all institutions to register Recombinant DNA Research with NIH should allay industry's concern regarding disclosure of proprietary and patentable information, since one governmental agency only would receive confidential information. As an additional benefit, retention of this section will provide the private sector an opportunity to demonstrate their social responsibility and enhance public credibility.

Another area of concern to us at the State level is that of major spills or transportation accidents of etiologic agents. As referred to on Page 33067 of the Federal Register Report, a team of experts from NIH and CDC could be formed to respond to emergencies of this nature. However, for a prompt and adequate response, it is essential that such a team(s) be formed and the names and telephone numbers of the members of such team(s) be published in the Guidelines for easy access in an emergency. Furthermore, the Guidelines should stipulate that some State Agency, such as the Health Department, be notified immediately in case of such accidents.

Finally, we propose that the following wording "and responsible State Agencies" be added to part IV-B-3-a-(4) so that it will read as follows:

> Provide timely notice to local institutions and responsible State Agencies when protocols, including modifications to on-going projects, do not conform to the standards in the NIH Guidelines.

Thank you for the opportunity to present these statements at the public hearing.

Sincerely yours,

Dhun B. Patel

Dhun B. Patel, Ph.D.
Environmental Scientist I
Biological Services

DBP:ds/st5-01

TESTIMONY OF

PHILIP L. BEREANO

ON PROPOSED REVISED GUIDELINES

FOR RECOMBINANT DNA RESEARCH

DHEW Hearing

September 15, 1978

I am Philip L. Bereano, Associate Professor in the Program in Social Management of Technology at the University of Washington in Seattle. My academic training has been in chemical engineering, law, and planning and I am a member of the New York Bar, and a former Commissioned Officer in the USPHS. For eight years I have been doing university teaching and research in the areas of science, technology, and public policy, first at Cornell University and then at the University of Washington. I have been a member of the University of Washington's Institutional Biohazards Committee which oversees recombinant DNA research since its inception. In addition, during this period of time I have been in communication with members of the staffs of Senate and House Committees considering DNA legislation, Dr. Fredrickson of the NIH, and ORDA, giving advice in regard to institutional and public policy aspects of the issues presented by research in this area. I also have been active in the Seattle area leading workshops for groups such as the ACLU, have appeared on a DNA panel at the annual meeting of the American Association for the Advancement of Science, and have participated in a number of presentations in the local media in the Puget Sound area.

Today I wish to comment on the public policy aspects of the Proposed Revised Guidelines for Recombinant DNA Research issued by the Department of HEW on July 28, 1978 and my testimony is being submitted on behalf of the Coalition for Responsible Genetic Research. I will be directing most of my comments to the materials covered under "Roles and Responsibilities" in the Proposed Guidelines, directing my remarks to the introductory statement by Secretary Califano that the Department is particularly seeking "comment on the sections in the proposed revisions that establish the mechanisms for administering and revising the guidelines." In fashioning my comments I will be drawing in particular on the experience of the University of Washington IBC.

In a commencement address at the University of Michigan in 1977, Secretary Califano pointed out that science has become too important to be left solely to the scientists. With specific reference to recombinant DNA research, he noted that policy deliberations in this area must be conducted with concern and deliberation; "this is the slowest way, the most inconvenient way--and in a democracy, the only way--to make such decisions." He went on to observe that decision-makers in science and medicine must learn the hard lesson that decision-making behind closed doors breeds distrust, even if what happens behind those doors is perfectly legitimate.

Although overall, the proposed revisions in the Guidelines are an advance over the existing Guidelines because of their increased clarity and evidence of some responsiveness to concerns which have been raised by members of the public regarding issues presented by DNA research, my comments will highlight what I perceive to be shortcomings in the document as published in the Federal Register; I am taking this approach in order to maximize what I consider to be the potential utility of my experiences and testimony for members of the hearing panel. I wish to make quite clear that my position should not be

interpreted as being "anti-science" or "anti-knowledge"; since I have been trained in the sciences and occupy a position at a university, my questioning of the procedures under which scientific research is conducted should not result in such implications.

My work in such areas as technology assessment has led me to understand that one of the most fundamental sets of questions that needs to be asked when considering new scientific and technological development concerns not only the attempt to anticipate the probable future consequences of such activity, but to attempt also to disaggregate those concequences by asking who actually would bear the risks associated with new developments, who would be paying the costs, and who would have access to the potential benefit. In regard to work in the area of recombinant DNA, it is clear to me that members of the general public fall into all three of such categories. Much, if not most, of this research is supported by tax dollars paid by the general citizenry; risks to health, safety, and the environment would be widely shared; and the benefits which have been suggested for such research would affect many sectors of society. Thus, I believe that members of the general citizenry have a fundamental right to participate in decision-making in this area, and a basic problem that I have with the proposed revisions of the Guidelines is that they do not recognize this situation nor facilitate access by individual citizens and their organized groups in the decision-making and regulatory process. Although it is commendable that scientists working in the area of recombinant DNA initially called the attention of the public and regulatory officials to issues raised by such research, in general the regulation of research in this area to date has been characterized by very limited opportunities for meaningful formal input on the part of such persons as scientists in other but related disciplines, non-scientific professionals with relevant perspectives, and ordinary citizens.

(The publication of the proposed Guideline revisions, along with an accompanying environmental impact statement, and the holding of these public hearings is a welcome change from such previous patterns.) The existing Guidelines developed by the NIH are essentially the product of deliberations conducted by those who will be regulated by them; thus the situation has potential conflicts of interest built into it, and should be as suspect as the attempts by industry trade associations to forestall meaningful government regulation by the adoption of voluntary industry standards. The existing composition of the NIH Recombinant DNA Advisory Committee (RAC), and most of the IBCs, heavily (in some instances entirely) composed of researchers in this area, justifiably does not lead to public confidence in their decisions. Considering the fact that the primary issues raised by this research are not solely scientific nor technological but have major public policy components, the existing situation goes against the grain of the past decade's academic research and findings in the area of "science, technology, and public policy" as well as recent political experience regarding the beneficial effects of citizen participation in many fields. The practices and experiences of the University of Washington's IBC are considerably more progressive than what is envisioned under the proposed Guideline revisions; as a result, when I reviewed the revisions I frequently thought how more limited and reduced in effectiveness the operations of our IBC would be if we were to be following the model proposed there.

I have organized my comments along four main themes: the social values raised by issues involving scientific research; the preferable roles in a democratic society for scientists and lay persons respectively to exercise in the regulation of research and its applications; the problems presented by having a single agency responsible for both the promotion and the regulation of an activity; and operational problems which I foresee if the

revised Guidelines were to be implemented as published. I will treat each of these below.

Science, Technology, and Social Value

A central feature of the traditional or "technocratic" view is that scientists and technologists are involved in activities which are removed from the realm of values, or else ought to be guided by values which are safe or conventional. The argument supporting the claim that science and technology are value-neutral usually includes an admonition that normative differences are really political and hence must be left to politicians and the political processes. I believe, on the contrary, that values are inescapable elements of any exercise of choice or decision-making, and since the conduct of research in an area like recombinant DNA is of such concern to members of the public and is to be regulated by the political processes, the assessment of the potential impact of such research and decisions concerning the direction of such research are permeated by opportunities for choice and hence issues of social value.

A concern for values is not merely the realm of philosophers or theologians. In fact, each of us in our daily lives is constantly dealing with issues of value. Values relate essentially to the process of labelling things "good" or "bad," or placing them somewhere along the spectrum between these two extremes. A social value is an affective conception of the desirable drawn from experience. No matter what individuals or institutions say their values are, values are really only made manifest by the actual processes of choice that an individual or institution undertakes.

For example, in the area of biological and medical practice, one of the oldest and most profound ethical admonitions is to primarily observe the command

to do no harm, and then subsequently to follow the goal of promoting the good. It is a source of wonder to me that such a powerful, although abstract, statement about the balance in goals to be pursued was formulated several thousands of years ago when humankind existed on the margin of survival. If anything, today when we are seeking to apply such precepts to a concrete situation--such as the conduct of recombinant DNA research--this teaching should be understood to have even stronger applicability. None of the benefits proclaimed as possible through the results of recombinant DNA research purport to take humankind from the margin of survival and provide it with basic security. Rather the good which is considered possible through such research would result in the improvement of an already tolerable situation. When I say that the current situation is tolerable, I am referring to the scientific and technological components of it; surely there is hunger in the world, and disease, and the like, but we should clearly understand that these are largely the results of political and economic factors, not scientific or technological ones. If those political, economic, and social factors are not directly addressed, no amount of advances in the area of DNA or other scientific work will, by itself, reduce world hunger or other ills. The extension of this ancient Hypocratic admonition to our present day implies that future generations have the right to require that we do not recklessly endanger the natural environment or the social fabric; there is not a similar imperative on us to present them with miracle cures.

Because the NIH Guidelines purport to deal with issues of safety, and to protect the general public and the communities adjacent to research to undue hazards, while at the same time allowing research to proceed which may provide human benefits, these ethical precepts should be reflected in the provisions of the Guideline revisions. I do not think they adequately are. First, I believe we should distinguish between the concepts of "risk" and "safety."

Based on the discussion in the book Of Acceptable Risk by William Lowrence (presently special assistant to the Undersecretary of State for Security, Assistance, Science, and Technology, and a participant in the March 1977 Academy of Sciences forum on recombinant DNA) we will understand risk as a relatively objective measurement of hazards, whereas safety is a subjective expression of the level of risk which is acceptable to a population. In other words, even if the various risks associated with DNA experimentation can be determined once and for all by an authoritative body (and, of course, we are nowhere near that situation at present), the question of safety involves many value issues which can only be articulated and developed by those members of the public which might be exposed to such risks and have the potential of access to the benefits of the research activity.

None of us lives a risk-free existence, and no one should be so foolish as to assume that such a thing is possible. Yet all of us make determinations, based on our own notions of safety, as to the level of risks we are willing to run--when we decide to travel by automobile or by railroad, when we decide whether to put on our auto seat belts or not, when we decide whether to smoke cigarettes or to cut down our consumption, and the like. Of course, some risks are involuntarily thrust upon us, and some commentators have suggested that people are one thousand times less comfortable with undergoing those risks than with ones which are voluntarily assumed. So, for example, we may say that the voluntariness with which a risk is encountered is an important consideration in one's determination of safety.

The NIH in effect recognizes these considerations. In the "Laboratory Safety Monograph" which is a supplement to the proposed Guidelines, is the statement that "any institution that has a need for an IBC must recognize that there may be legitimate concern in the adjacent community about whether adequate safeguards

are being taken at the institution to protect the general environment and community from potentially hazardous material" (p. 187). Clearly the "adequacy" of safeguards is a determination which is heavily value-laden. Yet, as I will maintain below, the Guidelines do not require adequate institutional mechanisms to insure that these value issues are resolved through the participation of the only persons who can legitimately provide insight into them--the general public which is affected.

In other places, the NIH is confused about the differences between risk and safety. For instance (FR 33084), there is the statement that "safety involving recombinant DNA molecules depends primarily on the individuals conducting the research activities." What the revised Guidelines apparently mean is that risks involving recombinant DNA research depend on the individuals conducting the research and the manner in which they conduct it. Safety is not their province alone; safety is a concern of the larger community, and in its determination the researchers have an important role to play in enlightening the local public as to some of the relevant factual information which may go into that determination.

On the same page in the Guidelines appears the sentence "motivation and good judgment [on the part of the researchers] are the keys to protection of health and environment." This statement, which introduces the Guideline's section on "Roles and Responsibilities," raises significant value issues. It is clear from experience under the existing Guidelines that--expressions and acts of scientific collegiality to the contrary notwithstanding--research in this area is intensely competitive and research groups are vying with each other for prestige and prizes. These are significant motivations of the researchers which the guidelines ignore in relegating to the researchers and to the institutional biohazards committee (which are so largely populated

by DNA researchers) the responsibilities for protecting the public.

To recapitulate, safety is not an objective determination. It is value-laden, subjective, and in a sense, political. The Guideline provisions do not provide adequate mechanisms for determining safety standards for recombinant DNA research, nor for implementing standards which are developed.

The Dangers of a Scientific Elite in a Democratic Society

Our current society has been characterized by many commentators as qualitatively different from those which have preceded it; for instance, the Harvard sociologist Daniel Bell has called it a "post-industrial society." One of the hallmarks of such a society, according to Bell and others, is that knowledge has become a source of power, much in the way that money in and of itself was a source of power in earlier societies, or a noble title in societies preceding those. Knowledge about scientific developments, as well as access to the technological implementation of such scientific information, have become political commodities. Those who dispense the benefits of scientific and technological development become important power holders in our society.

Although, as I have noted, scientific researchers in the recombinant DNA area have gone considerably beyond what has traditionally been the norm in informing the public about the implications of their work, I believe that the experience to date with the regulatory processes has still been inadequate. An "old boy network" exists and flourishes in the DNA field and would not be significantly ameliorated by the instances of public participation contained in the new Guidelines.

This is most glaring in regard to the composition of the IBCs.

Probably the most significant aspects of the guideline revisions, in terms of public policy and administration, is the delegation of basic regulatory authority from the NIH to the IBCs. NIH is clearly within its authority to mandate certain standards about the composition and functioning of the IBCs, and I believe that the Guidelines are inadequate in this regard. (See FR 33085.) I have participated in research activities investigating the composition of existing IBCs. Others here today will testify in greater detail about these findings, but for now let me state that most IBCs, if not all, are hopelessly demographically skewed. They are totally non-representative of the communities whose safety and interests are concerned. They are overwhelmingly (and in some cases exclusively) male, white, graduate degree holding, and the like. I make this accusation against my own IBC, although we are composed in a much better fashion than committees at most other institutions.

The Guideline revisions would perpetuate this situation. They require that committees contain members from "disciplines relevant to recombinant DNA technology, biological safety, and engineering." No other disciplinary areas, and no areas whatsoever of human experience that cannot be categorized by some academic disicpline, are required at all on a committee which is supposed to make determination about public health and safety. The Guidelines only "recommend" that the IBC also include "members knowledgeable about such matters as applicable law, standards of professional conduct and practice, community attitudes, and the environment" as well as "at least one member [to] be a nondoctoral person from a laboratory technical staff." The only other requirement is that "at least one member shall not be affiliated with the institution" but for membership on the IBC. I submit that this is wholly insufficient. First, there are other areas of expertise which are

clearly as important as engineering and the rest--for example, the policy sciences. Secondly, there are general areas (which I would not call disciplines) which are essential in any attempt to determine safety--community leaders who are in touch with grassroots attitudes, for example, should be mandated on IBCs, environmental groups which have been diligent in public interest protection of the environment are in the best position to present those concerns for an IBC's deliberation, etc. Third, a "non-doctoral person" could be a graduate student under the tutelage and presumably the direction of a DNA principal investigator; the guidelines should clearly mandate IBC membership by a laboratory technician or other working person. Fourth, requiring one member of the IBC to be unaffiliated with the institution smacks of tokenism. Every large institution has dozens of persons around who maintain no formal affiliation, and draw no salary from it, but whose social and professional relationships are so intertwined with those of the institution's administrators as to have an identity of viewpoints. The discussion by Director Fredrickson (FR 33065) of this matter does nothing to assuage my fears in this regard. Finally, the guidelines should mandate membership on the part of a public health offical (if the local authorities, of course, agree) rather than just suggesting cooperation; under our constitutional system, the fundamental responsibilities for protection of the public health and safety ("the police power") reside with the state, which may have delegated such responsibilities to local jurisdiction. In no way can the NIH Guidelines usurp this authority, and indeed they should recognize it fully in the provisions for IBC membership. Membership by local governmental officials on the IBC would facilitate recognition of the largely political character of some of the IBC decisions. Let me emphasize that I see this as a positive factor, not something to be avoided or circumvented.

Because the decisions of the IBC will contain elements dealing with safety and other policy determinations, elements which are largely "subjective," value-laden, and political, we should recognize that the aim as regards the competence of such groups is for wisdom, not merely knowledge. Knowledge, in the sense of scientific information and fact, is an essential but insufficient component of the information which must go into the deliberations of the IBCs. Wisdom encompasses knowledge but is broader. The committees contemplated by the Guideline revisions would not possess the necessary competence to effectively carry out their mandate. They should be required to have a demographic distribution which somehow reflects the communities in which they are located, as well as possessing the necessary scientific expertise, in order to blend these two aspects of the decision-making processes they will be engaged in. Thus there should be requirement as to the distribution of committee members by age, sex, income level, professional background, and other demographic variables. In addition, many individuals who would be necessary for membership on such committees are not currently being paid for the time and effort which they would be devoting to such an activity. The guidelines should require compensation for those individuals for whom service on a committee would be a financial difficulty, especially insofar as they would take time and energy which these individuals would otherwise have to expend in supporting themselves and their dependents.

I should mention in passing that the insistence in the guidelines that IBCs be understood as referring to "institutional biosafety committees"rather than "institutional biohazard committees" as they have been known for some time, smacks of the grossest kind of doublespeak and euphemism. The Director's comment.(FR 33064) that "I have decided to change the name of the biohazards

committees to biosafety committees to reflect the spirit of the guidelines more closely" is a reason without substance, and sounds like propaganda unworthy of this Department.

Separating the Promotional and Regulatory Functions

Government involvement in DNA research has been following the "AEC pathology" in failing to institutionally separate promotional agency activities from regulatory ones. Unfortunately, the new Guidelines would not adequately address this syndrome. The intertwining of regulatory concerns with promotional activities is a further extension of the "old boy network" suspicions I have referred to above, and reminds us of the widely-discredited situation which existed for many years in regard to nuclear power. Since the government has recognized what citizen groups have been saying for many years—in regard to atomic energy—and has established separate agencies to deal with these two different aspects of the situation, it is high time that similar procedures were begun regarding recombinant DNA. Promotion of a technology results in the vesting of professional, as well as of economic, interests in the application and exploitation of that technology. The expectations we have of regulators are far different from the types of commitments associated with promoters. In this regard, it is noteworthy that governmental decisions about recombinant DNA are being more explicitly made at the Departmental level rather than at the level of the NIH. But the AEC pathology should be recognized more directly and dealt with more satisfactorily.

My concerns here are similar to those I expressed above in regard to the technological elite: how to assure that in a democracy decisions affecting members of the public are made democratically. As an example of the insufficiency of the Guideline revisions in this regard, I would refer to the Director's

discussion of the RAC (FR 33066) where he acknowledges having received many comments urging that the composition of the RAC be significantly broadened. (Much of the above discussion regarding the membership of the IBCs is relevant here and in the following observations.) His statement that more public representation on the RAC might be desirable, "including perhaps a 'dissenter' from current NIH policies" again suggests tokenism or a kind of condescension which Herbert Marcuse has labelled "repressive tolerance" (that is to say, the appearance of liberality without its substance). Is the NIH so sure that its grantees and minions have all of the necessary wisdom in this area to fully assess the risks and make safety determinations regarding desirable courses of action? Is the government so completely prejudging the regulations and their political implications that it offers merely one slot on the RAC as an act of charity and graciousness, to those who have deep concerns about the directions of the existing policy?

In the areas of environmental policy and regulation, the courts have recognized the critically important role which citizens groups and environmental organizations have played in holding public officials to the highest standards of duty and in contributing to the substantive protection of environmental values; it is high time for the NIH and the Department of HEW to recognize that those among us who have been raising questions about the substance and administration of the regulatory procedures under which recombinant DNA research has been occuring have performed an important public interest service. Our membership and participation on the RAC and on institutional biohazards committees should be actively sought as a means of attempting to further achieve the goals of safe and effective policy making and regulation in this area.

Operational Difficulties in Implementing the Proposed Guidelines

(1) Delegation of authority. Up until now, controls on recombinant DNA research have been based largely on principles of self-regulation and peer review. As noted above, experience during the past year at two prestigious schools has shown that irresponsible or thoughtless actions can occur under this form of control. However, the response of the NIH in the Guideline revisions has been to propose to enhance the responsibilities of local institutions rather than to balance or safeguard against such irresponsibility. At this time, I do not believe that sweeping delegation of authority for initial approval of experiments should be made from the NIH to IBCs. My comments above about the unrepresentative composition of IBCs, both to date and as contemplated under the revised Guidelines, are relevant here. In addition, the whole question of the most appropriate balance of authority between a central federal agency (which could assure that requisite technical and policy considerations are brought to bear on aspects of the regulatory process) and local IBCs (which could assusre sensitivity to local conditions and provide extended means of public participation in the regulatory process) needs to be further developed.

The Guideline revisions require (FR 33085) that "the committee has the experience and the expertise to assess the safety of proposed recombinant DNA research projects and any potential risks to public health and the environment." Again let me emphasize the distinction between risk and safety which I made above. While I believe that IBCs can have the competence to assess safety, the assessment of risk is another matter. Risks generally

would not vary from location to location, and therefore the assessment of risks involved in recombinant DNA work should best be performed by a single body. My experience on an IBC leads me to believe that none of these committees has the competence, time, or resources to do adequate risk evaluation.

Members of IBCs are primarily going to be employed in other capacities or have other substantial responsibilities to their families, communities, and the like. Members of the IBCs are not themselves full-time personnel involved in risk assessments, laboratory inspection, training program certification, or any of the other kinds of substantially time-consuming activities for which the Guideline revisions purport to give them responsibility. For most committee members, this is an "add-on" activity, although one which may be undertaken with the highest considerations for its seriousness and public importance. Nonetheless, virtually none of us on the University of Washington IBC, other than DNA researchers themselves, on a regular basis go to DNA laboratories to ascertain whether the Guideline procedures are being followed, sit in on training programs, and make judgments as to the competence and training of individual research personnel, etc.

As a result, although the Guidelines require that the institution assume responsibility for assuring compliance (section IV-A-1-d), in fact most institutions and their IBCs are unable to do so; even if they were to attempt to carry out this function, how will the NIH know that the institution is adequately fulfilling it? Administratively, this situation is central to the Guidelines, and yet it is essentially a set of "paper platitudes." Let me provide several examples from my own IBC experience. Under the current regulations, it is forbidden to eat food in a P-2 laboratory. Yet, students of mine have dropped in at P-2 laboratories at noontime and found personnel eating lunch at the

bench. Another example: a researcher of the highest repute in our institution has admitted that frequently in his laboratory he neglects to wear his laboratory gown; an item of trivia, except that the classification on his laboratory is such as to require the wearing of such garb.

Such examples indicate that one of the most significant avenues of danger in the conduct of this research, and one of the most significant problems with translating paper requirements into real protections for local communities is that arrogance or familiarity can breed carelessness. Certainly, members of the IBC cannot regularly monitor what is going on in DNA laboratories, and in fact the staff of the biohazards offices at most institutions are completely inadequate to do so on any systematic basis either.

Furthermore, in attempting to fulfill the above mandate quoted from the proposed Guideline revisions, how can local IBCs make the sort of safety assessment and risk determinations they are expected to make when on the national level these questions are still the objects of much controversy, and when the NIH itself to date has followed a policy of allowing research first and risk assessment afterwards (much like the situation described in Alice in Wonderland). Not only is this scarcely good and orderly science (leaping over areas of insufficient knowledge--such as whether particular recombinations occur in nature, and if so with what frequency) but it is not good and orderly administration either.

The Guideline revisions require (FR 33085, section IV-A-2-a-(ii)) that the IBC responsibilities include "review and approval of facilities, procedures, practices, and the training and expertise of recombinant DNA personnel." Unless the members of the IBCs are going to spend essentially full time performing the functions of such membership, how are they supposed to carry out these responsibilities? The NIH Guidelines set up a standard of activity and responsibility which the IBCs at most institutions are totally unprepared to

carry out. If the University of Washington is at all representative, it must be said that we have virtually no resources at our disposal to conduct such activities, we have no personnel under our direction that we can require to assist us in performing such functions, and essentially no budget for our operations.

Indeed, the NIH revised Guidelines are remiss in requiring such significant responsibilities of the IBCs and not requiring adequate fiscal support for them. At the very least, the NIH should require that a percentage of the overhead which is charged on DNA research proposals to the NIH be earmarked for operations of the IBC, and that the IBC be provided with adequate budgetary and administrative support in carrying out these responsibilities, as a condition of institutional funding by the NIH. It is true that these concerns have been raised to the NIH before, but the Director's comments (FR 33065) on this regard do not solve the problem. He has assumed that because the government research grants contain an overhead factor, therefore the NIH is already paying for the operation of such committees, but I can assure him, and the hearing panel in general, that the committees never see such funds, and that there are severe budgetary limitations on the IBCs in carrying out the functions expected of them.

The University of Washington IBC has been carrying out many of the functions which the guidelines envision, however. Among these are development of procedures for certifying actual laboratories as meeting the levels of physical containment claimed for them; participation in the development and certification of training programs to insure that researchers carrying out recombinant DNA work are aware of what the regulations require of them and have the capabilities to carry out those requirements; passing on the qualifications of specific researchers to actually carry out the research

programs (this is especially important in regard to the more risky types of experiments, such as those proposed at a P-3 level).

(2) Institutional policies beyond the guidelines. Section IV-A-2-a of the Guidelines (FR 33085) defines the responsibilities of the IBC as to "review and, if in compliance with the NIH Guidelines, approve the initiation of all proposed recombinant DNA research conducted at or sponsored by the institution receiving NIH funds for any recombinant DNA research." This is an expansion of the earlier statement (section IV-A-2) that "the principal functions of the IBC are to review and oversee all recombinant DNA projects and to advise the institution and ORDA whether the proposals and the research comply with the NIH guidelines." However, none of this language expresses NIH recognition, nor provides notice to investigators of the possibility that an instituion may institute policies in addition to, or going beyond the requirements of, the NIH guidelines. NIH should recognize these institutional prerogatives and should indicate its willingness to respect the exercise on the part of the institution of policy considerations which go beyond the letter of the Guidelines. This should be done to provide notice to the institutions and to the investigators, and is in accord with the introduction to section IV which acknowledges that the Guidelines "will never be complete and final, since all conceivable experiments involving recombinant DNA cannot be foreseen" and also that "the guidelines cannot anticipate every possible situation" (FR 33084).

I would suggest that the language of (ii) be changed to something along the lines of the following: "review all proposed recombinant DNA research conducted at or sponsored by the institution receiving NIH funds for any recombinant DNA research to ascertain compliance with the NIH Guidelines and with any institutional rules, policies, guidelines which may have been adopted to regulate such research, and on the basis of such review, vote its approval,

disapproval, recommended modifications, or conditional approval, of such research proposals." In addition, the Guidelines should state that no such recombinant DNA research proposal will be funded by the National Institutes of Health unless it has been approved by the institutional biohazards committee.

In expressing these concerns, I am pleased to note that Senator Adlai E. Stevenson, who is chair of the Subcommittee on Science, Technology, and Space, and has conducted hearings on recombinant DNA research, agrees with this position. In a personal communication to me (June 1, 1978), he notes that local discretion in enforcement is necessary, and goes on to say "moreover, I assume that institutional committees will retain even broader authority to approve and disapprove projects or to attach conditions to their conduct." I urge the NIH to modify the Guidelines accordingly.

As example of the kinds of policy which the University of Washington IBC has used in the past, let me offer the following: the imposition of a moritorium on considering P-3 level research proposals (for approximately 18 months) in order to assure that researchers in relevant areas, members of the IBC, biohazards safety personnel, and the general public could build up sufficient experience with less risky forms of experimentation in order to have the capabilities to reasonably assess, perform, and monitor more risky experiments; conditioning our approval of a particular experiment on the requirement that the researcher perform certain intermediate tests on the mutant E-coli produced in the experiment and report back to the committee if certain indicators were present; conditioning the approval of proposals involving the use of virulence genes to require that they be split in ways

which would increase the probabilities of the fragments being kept non-virulent; conditioning approval of proposals involving the use of non-transmissable plasmids to require checking that they remain non-transmissable after cloning; and conditioning approval of an experiment involving genetic transfers from yeast to E-coli and then back into yeast in order to study what the effect has been, on the prior approval by the NIH for the use of yeast as a host system. None of these conditions, to the best of my understanding, are required by existing NIH rules.

What the IBC can do in actuality is to assure that there is good flow of information between the public and technical personnel. This helps to insure that their own deliberations are as well informed as possible, and keeps the members of the resarch community and of the general public in some type of reasonable communication. In order that such functions proceed smoothly, certain procedural requirements have seemed to us at the Unviersity of Washington to be essential. I note them here with the suggestion that the NIH require them as procedural rules for all IBCs. Meetings of the IBCs should be open to the general public (except perhaps for the actual voting on particular research proposals); furthermore, the general import of "sunshine law" requirements should be followed, assuring that there is adequate publicity of the open meetings, that minutes are publicly available, etc. In addition, at the University of Washington, we have decided to hold our meetings in the evenings so members of the working public and homemakers can attend; we require that researchers prepare a lay summary of their proposals in written form for distribution to members of the general public which come to our open meetings where their proposals are being discussed; that they orally present their research proposals in terms which are understandable to members of the lay public and to the

members of the IBC who are not themselves DNA researchers; and finally we require that votes to approve MUAs be by an extraordinary majority, in order to signify to the general public that a substantial proportion of the membership of the IBC believes in the safety and efficacy of the proposal at issue. I urge that the NIH incorporate such rules as requirements for the functioning of all IBCs.

(3) Other insufficiencies and inconsistencies. The Guidelines correctly reflect a concern for the due process rights of researchers and investigators. They are remiss in not similarly reflecting a concern for the due process requirements that laboratory workers and the general public have the right to expect from this regulatory process.

Although the Guidelines are quite elaborate, the section on sanctions are rather terse and slender (section IV-D-1, FR 33087). I believe that administrative law has developed a much more wide-ranging set of possible sanctions which should be considered by the NIH for possible use in regard to violations of the Guidelines. My concern here is that the sanctions provided in the revised Guidelines are neither flexible enough nor credible enough to achieve the aims of compliance and smooth operation.

The guidelines should require that practices within institutional laboratories comply with OSHA standards, and the standards of any state agencies concerning occupational health and safety. Although it is true that this is not legally necessary, having note of it in the Guidelines would perform the salutary functions of (1) acknowledging that NIH is seriously concerned about the health and safety of laboratory technical personnel in this whole matter, and (2) reminding the principal investigators (if not the institutions) who might be unaware that their activities fall within the perview of the OSHA rules that this is in fact the case.

An institutional biohazards safety officer should be required to be on an IBC or to work in close association with it (even if only P-1 and P-2 work is being performed at the institution). As noted above, the way that the revision contemplate constituting IBCs, virtually none of the actual members (other than perhaps the DNA researchers themselves) will have the expertise nor the time, etc., to actually ascertain complaince. It is inconsistent to require certain levels of due care (the physical safeguards) and to require that the IBCs assure compliance with this, without also requiring that the IBCs contain the competence to do so.

The ORDA is required (in section IV-B-3-a-(8)) to review the membership of the IBC. However, the Guidelines in no way provide any criteria for ORDA in terms of carrying out this function, nor do they indicate what kinds of sanctions, if any, ORDA can bring to bear against an institution which has a committe which is not deemed in compliance. This section of the Guidelines should be elaborated in some additional detail.

The Guidelines themselves contain virtually nothing on RAC membership, although it is recognized as a problem (FR 33066). It is true that the Director acknowledges that the RAC is to be primarily a technical committee, but its functions actually go beyond this to encompass matters of public policy. (See Director's discussion, FR 33067-8.) As a result, the NIH should either have two committees to advise it (one as a technical committe and the other to examine non-technical policy questions) or the RAC should be definitively re-constituted in order to deal more effectively, and in a representative fashion, with the broader issues of social responsibility and control which are presented by the public policy aspects of its decisions. If the latter instance is followed, clearly additional public members need

to be appointed to the committee. In addition to these considerations the public should be assured that the committee will function without the sort of blatant partisanship which has characterized some of the actions of the present chairperson.

There is one portion of The Director's Decision (FR 33044) which highlights some of the fundamental failures of the NIH to come to grips with the nature of the problems presented by DNA regulation. It is a demonstration of a failure to understand the probablistic nature of risk to imply that because harm has not in fact occurred that it is less likely and that the "burden of proof" should therefore shift regarding attitudes to vigilance. The footnote citation to a March 1978 Subcommittee report of the House Committee of Science and Technology ought to be carefully analyzed. "The burden of proof of safety factors should not be borne exclusively by proponents of recombinant DNA research; opponents must assume a corresponding burden," it states (FR 33047). The most important element of this statement is the qualifier "exclusively." The main thrust of the academic work over the past decade in the area of science, technology and public policy, and in the development of the notion of technology assessment, is that the proponents of technological change, who would be thrusting impacts on affected parties, should, in the main, bear the burden of proof in assuming the risks, etc. The Director's remark is highly ironic to those of us who have been attempting to raise social policy issues, or have been questioning the unseemly haste with which some of the research is being conducted and the attendant pressures which have been put on the regulatory system. We feel we have been bearing a heavy burden for the past several years; our resources are slender and our access to information has been limited; our desire has been to assure that research in the area is safe, not to "restrict" it, as the Director claims. We feel that any

notion of shifting of the burden of proof in regard to these policy issues is premature, and we fear that it may be a prelude to a significant weakening of regulatory protections. It should be eliminated.

Overall, my concerns here are that the protections in the guidelines are largely "paper protection." There is no effective mechanism provided to assure that they are realized in the day-to-day operations of the regulatory process. In fact, I would argue that it is good that additional requirements be placed on the IBCs so that "the runaway shop situation" is not encountered--i.e., using the analogy of the environmental regulatory situation, that researchers cannot claim that regulatory restrictions are too onerous in location X and that they will therefore pick up and run off to location Y. The public is concerned enough about some of the major advances and activities in biological research areas to want a level of assurance as regards its concerns for health, safety, and environment protection which, in an operational manner, these guidelines do not provide.

UNITED STATES DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
PUBLIC HEARING ON THE PROPOSED REVISED GUIDELINES
FOR RECOMBINANT DNA RESEARCH

HUBERT H. HUMPHREY BUILDING
WASHINGTON, D.C.
SEPTEMBER 15, 1978

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Presented by
DEBORAH W. FEINBERG
Environmental Scientist

My name is Deborah Feinberg and I am the Environmental Scientist for the New York State Attorney General's office. I would like to thank the Department of Health, Education and Welfare for this opportunity to comment on the Proposed Revised Guidelines for Recombinant DNA Research.

The Proposed Guidelines under discussion today constitute a substantial downgrading in containment from the original National Institutes of Health (N.I.H.) Guidelines. This office believes that such a reduction in containment levels is not warranted by scientific evidence. We therefore recommend that the original NIH Guidelines remain in effect.

The Proposed Revised Guidelines contain a number of assumptions to which we take exception. My office strongly objects to the statement by the Director of N.I.H that those concerned with the potential hazards resulting from recombinant DNA activities now bear the burden of proof to show such hazard (p. 33097). This and other statements purporting the safety of recombinant DNA research, which are directly reflected in the reduced containment levels, are not substantiated by empirical data. There is no basis for downgrading the Guidelines based on experimental results. That we have as yet not experienced an instance of pathogenicity resulting from recombinant DNA

activities is not proof of safety. We are in much the same position today as we were at the beginning of this technology: blindly mixing the genetic material of organisms that would not accomplish such exchanges naturally. We have no substantial facts or data to justify these lenient Guidelines and there remain good grounds for suspecting hazards from this new technology. Unproven confident statements of safety should not be accepted as a basis for easing the Guidelines.

The Proposed Guidelines do not adequately take into account ecological considerations. A great deal of concern has been expressed over the possibility of creating an epidemic while the more likely possibility of inadvertently disrupting the ecological balance has been overlooked. A recombinant organism need not only produce a pathogen to cause harm. If an organism gains a slight competitive advantage by producing more of an enzyme than does the wild type, it could conceivably alter the balance of an ecological system with grave consequences. Before we relax the Guidelines we must assess the potential harm of an recombinant organism not just to man but to plants, animals and the environment. We can have no assurances of safety until we understand the mechanisms of pathogenicity and how an organism will interact in a complex ecological situation. At this time we can not answer such questions and consequently we should not attenuate the Guidelines.

The Proposed Revised Guidelines exempt from compliance non-novel exchangers (P. 33070). The rationale behind this exemption is that such exchanges take place in an unregulated manner in nature. There are two objections to this exempt category. First, given that one member of a genus is known to exchange genetic material with an unrelated species in nature, we should not extrapolate that all members of that genus should be exempt. We must ask whether other members of the genus would meet this organism in a natural setting. Also the extent of interspecies exchange within a genus should not be assumed without experimental basis. As such, the exemption list is too broad.

Second, the rationale for these exemptions ignores basic ecological considerations such as natural rates of exchange, simultaneous occupation of ecological niches and the effects of concentrated products of such non-novel exchanges in the environment. If one piece of DNA is exchanged naturally, that does not mean that the transfer of any segment of DNA from that organism is safe. Similarly if the organisms exchange DNA in a limited manner, increasing the rate of exchange could result in the concentration of an enzyme or hormone within an organism with unknown results. In the laboratory we do not reproduce natural conditions. We place organisms together that might only rarely find themselves in close proximity in nature. We must not

only consider the effects of producing a toxic substance through recombinant techniques but also of concentrating a naturally produced substance or increasing a rate of an exchange that might happen only rarely in nature. Until we can anticipate the results of altering an established ecological balance, such experiments should not be exempted from the Guidelines. This same consideration applies to self-cloning experiments exempted by the Guidelines. The Environmental Assessment section acknowledges that hormones and enzymes are among the proteins that might prove harmful to other organisms (p. 33103). Amplifying a naturally occurring protein within an organism should not a priori be accepted as a safe experiment to be exempted from regulation. We need to know much more about its interaction in a natural setting before we discount its risk.

The Proposed Revised Guidelines exempt recombinant DNA experiments using naked DNA on the grounds that it is "extremely unlikely to be hazardous" (p. 33107). In addition, containment experiments involving animal cell transforming viruses have been substantially reduced based on the supposed inefficiency of infection by naked DNA. Both these decisions do not take into account the results of the Rowe-Martin risk assessment experiments with polyoma virus which were reported at the Falmouth Conference. This experiment showed that naked polyoma DNA, when injected into the bloodstream or tube-fed into

the colon of mice caused low-level infection. Not only was naked DNA shown to be an infective etiological agent, it can also be envisioned that such an experiment would expand the host range of polyoma by allowing the polyoma DNA to infect a cell that would be unreceptive to an encapsulated virion. Rather than lower the containment levels for recombinant work with viruses, this experiment should encourage us to maintain the original stringent containment levels for such viruses.

The Proposed Revised Guidelines delegate substantial authority and flexibility to individual Institutional Biohazard Committees (I.B.C.) and as such lay the foundation for inconsistent protocols around the country. The IBC's are given the authority to choose between various containment combinations and to reduce containment levels, at their discretion, by one step for well-characterized clones. Such a system will inevitably lead to non-uniform compliance and a subsequent disrespect for the NIH Guidelines. While IBC's should take some of the burden from the Recombinant DNA Advisory Committee and help organize protocols consistent with the NIH Guidelines for its member researchers, it should not be entrusted with such vast federal administrative power. Researchers and IBC's should follow uniform Guidelines, not decide them. This applies equally to the inspection and

oversight responsibility given to the IBC's. It is the duty of NIH to administer a grant program and to insure compliance with the Guidelines. This role can not be delegated to its grantee institution without raising serious conflicts of interest.

The rationale for switching physical and biological containment levels is not adequately explained. The method for quantifying containment levels is unclear and could give the impression that the decision to allow this was based on researcher's convenience rather than on empirical analysis.

Similarly, the rationales for lowering containment levels for shotgun experiments and exemptions from the ten liter limit are unclear. In the latter case, once again, ecological factors are ignored as this limitation only applies to recombinant organisms known to make "harmful products" (p. 33107). "Harmful products" must not be defined too narrowly. The proper questions to ask in assessing ecological harm include the following: If introduced into different environments would it cause changes in species composition, would it alter the existing balance of plants and animals, would it outcompete a natural resident of a niche? These are the factors that must be considered in assessing harm.

We recommend that the membership of the Recombinant Advisory Committee be expanded to include a greater proportion of representatives of the public interest and individuals with knowledge in public policy and technological impact on society. The decisions made by the RAC extend beyond strict technological assessments. They involve the social impact of a vast technology and therefore should have members representing all aspects of its decision-making functions.

We also recommend that the Institutional Biohazard Committees expand their membership to include representatives of the State or equivalent local Health Department as well as a member of the laboratory workers engaged in the recombinant DNA research.

The Proposed Revised Guidelines leave the system of medical surveillance up to the discretion of the individual institutions. The nature and extent of the medical surveillance system is left vague. We recommend that a biohazards officer be appointed at each institution, not just for institutions engaged in P3 and P4 level work as required in the Proposed Revised Guidelines, and with the cooperation of the institutional biohazard committee develop specific medical monitoring and record-keeping plans. The medical surveillance plan should include full medical histories, periodic medical checkups and samples taken of blood serum, intestinal flora or, depending on the agent being worked with, whatever is most

appropriate to detect physiological changes. The surveillance system should also maintain accurate records on incidence of illness among all recombinant research personnel, all incidents of accidents, spills and recombinant organism releases,and the location and conditions of recombinant DNA organism containment. These records will be particularly important if it should become necessary to establish legal liability at a future date in case of an accident or sickness. No N.I.H. grant should be awarded until an adequate plan of medical monitoring and record keeping is prepared. A central clearinghouse should be established at the federal level to which copies of all medical surveillance plans and records should be filed. Such a clearinghouse containing records of all recombinant organisms, accident reports, and medical records would be invaluable in ascertaining biohazard risks from recombinant research, and establishing safety records of particular laboratories and containment methods. In the event a hazard is detected, other institutions working with similar organisms could be quickly notified. A central record-keeping center would also provide important statistical and epidemiological information for future studies.

Detailed emergency plans should be drawn up by the biohazards officer and the IBC for each recombinant DNA project. Such plans should be submitted to the N.I.H. for approval along with the grant application and be stored in the central clearinghouse.

In the event of any release of recombinant organisms or of non-compliance with the Guidelines, the state or local health authorities should be immediately notified. The effects of any accident will be first experienced within the local surroundings. Consequently, the State Health Department or its local equivalent should be informed at all times of what organisms are being used, and of all releases of recombinant organisms, even those considered minor. The Health Department representative should be an active participant in biohazard assessments as well as remedial emergency activities. We also recommend that in addition to providing advice, a Center of Disease Control Strike Force be organized which will be ready to act in the event of an emergency.

We recommend that grievance procedures for workers be established under the Guidelines. The Decision document states that OSHA regulations already provide such a mechanism. In fact, however, the OSHA regulations covering this area do not apply to state or local governments and as such would not apply to recombinant DNA research conducted in many state universities. A specific protocol to deal with charges of both willful and negligent non-compliance should be established by the NIH. This protocol should detail how and to whom charges should be brought,

opportunity for defense against charges, and protection against discrimination of the party bringing charges. Such grievance mechanisms should be established and publicized to all recombinant DNA workers to facilitate the reporting to NIH of Guideline violations.

To summarize, the New York State Attorney General's office believes that there is no scientific justification for the relaxation of containment levels contained in the Proposed Revised Guidelines. On the contrary, the expression of eukaryotic DNA in bacteria exhibited in such experiments as the successful insulin production work, prove that higher and lower organism gene boundaries can and will be crossed by man. The Rowe-Martin experiment shows that naked DNA, far from being inactive, does infect cells. Unsubstantiated claims of the safety of recombinant DNA research pervade the Director's Decision document and the Environmental Assessment document and are reflected in these newly proposed Guidelines. We strongly believe that the containment measures are too lax and should be increased in order to protect health and environment.

By delegating increased authority to institutional biohazard committees and allowing them wide discretion in setting containment levels, the Proposed Guidelines ensures

confusion and disrespect in the implementation of the Guidelines. A uniform set of Guidelines is a necessity for the safe conduct of recombinant DNA research. No empirical justification for choosing between containment level combinations is offered and this approach should not be accepted without a full explanation.

Finally, provisions for the enforcement of the Guidelines are inadequate. NIH should enforce the Guidelines and monitor its grants for recombinant DNA research. Yet, the revised Guidelines delegate responsibility for inspection, oversight and even choice of containment levels to the Institutional Biohazard Committees. This we believe is an improper abrogation by NIH of its duty to administer its grant program. Enforcement of the Guidelines cannot be left to the institutional beneficiaries of the grants. There is an obvious conflict of interest. Instead, NIH should allocate sufficient funds towards the administration of its grant program providing for personnel and equipment to inspect grantees. If NIH will sponsor this research, it has the duty to ensure that recipients of grants comply strictly with the rules. In a broader perspective, legislation is required to make the Guidelines applicable to non-NIH grantees and to impose effective penalties for non-compliance. New York State recently

passed legislation to insure compliance of the Guidelines with provisions for laboratory inspections, penalties for Guideline violations as well as training and medical monitoring of personnel. The federal government should do no less.

In conclusion the New York State Attorney General's office believes that the Proposed Revised Guidelines serve to reduce containment levels and at times exempt altogether experiments that have not been proven to be without risk. We can see no reasonable justification for this downgrading of containment. We have as many unanswered questions regarding the ultimate consequences of recombinant DNA technology today as we did at the start of this technology. We are here to protect the health and environment of our citizens. Let us not be derelict in our duty.

FRIENDS OF THE EARTH

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David Brower, *President*

September 15, 1978

WRITTEN COMMENTS BY PAMELA LIPPE, ASSISTANT LEGISLATIVE DIRECTOR, ON THE PROPOSED REVISED GUIDELINES FOR RECOMBINANT DNA RESEARCH

I. Introduction and Overview

We in the public interest community look at recombinant DNA as a powerful new technique and technology with unprecedented potential for benefit and harm. Contrary to recent scientific pronouncements, we do not wish to stop recombinant DNA research or scientific progress; we simply wish to achieve the benefits without incurring unnecessary risks.

The scientific community looks at recombinant DNA as a powerful tool which will allow them to answer questions beyond their previous understanding, and to do things that stretch the limits of their imagination.

While it is understandable that scientists more clearly perceive the beneficial aspects of their efforts, a quick survey of recent scientific and technological breakthroughs illustrates the time bomb and elusive nature of many of science's most cherished dreams.

As the Stevenson subcommittee pointed out in its recent oversight report, "At issue is the extent to which research scientists should be entrusted with responsibility for their own conduct, individually or through peer review, or be subjected to external control and scrutiny."

Our position is that if the situation is serious enough to develop guidelines for the conduct of this research, then it is serious enough for the guidelines to be enforced. Self-regulation has never worked in the past. There is no reason to expect that recombinant DNA is to be any different.

In general, my comments will focus on the procedural aspects of the guidelines as requested by Secretary Califano. I hope that you find these comments and recommendations useful.

II. Scope and Applicability

We support efforts to further extend the guidelines to the private sector such as those in the proposed revisions. It is unfortunate that no more comprehensive mechanism exists to transform the guidelines into full-fledged regulations -- legal authority extending to industry and academia alike, and to both effectively.

We would still urge that HEW use Sec. 361 of the Public Health Service Act. Congressional inaction on this issue does not in any way diminish the need for meaningful regulation in this rapidly developing new field. It was "hard ball" politics, not new data that killed both the Senate and House bills.

The new data discovered and/or developed in only one year's time offers assurance about one small part of the potential danger -- e. coli k-12. We are already considering approval of new host-vector systems, deliberate release into the environment, and exempting research with wild-type e. coli. What little we know now, will become even less as we continue to open broad new biological and ecological vistas.

We urge you to reconsider your decision regarding Sec. 361 in light of the inadequacy of the existing NIH proposals, and the need for legally enforceable regulations due to increasing interest in the private sector. Even if Congress acted next session, which is far from certain, it would be a minimum of two years before regulation would be in place. The drawbacks of that course of inaction far outweigh the use of Sec. 361.

Recommendations:

1. Promulgate the guidelines as regulations under existing authority.

2. In the absence of full regulation under existing authority, NIH funded investigators should require an approved MUA with certification on file with the NIH, prior to shipment or transfer of recombinant DNA materials.

3. The guidelines should apply to all recombinant DNA research at institutions receiving <u>any</u> NIH funding.

<u>Exemptions</u>

The requirement for the fourth class of exemptions is that they "exchange DNA by known physiological processes." "Known" is a much broader class of exemption. How does the NIH define it? More significantly, there is no requirement that that particular class of exemptions be "safe."

The Decision of the Director (p 33044) says that "provision will be made for public input either by announcement of proposed exemptions prior to consideration by the Recombinant DNA Advisory Committee, or before a decision by the Director becomes effective." Obviously, the second alternative is totally inadequate. A procedure must be developed to allow for public notice and opportunity for input before the decision is made (ie. before the RAC has considered it.)

Recommendations:

1. "Known" should be changed to "natural."

2. All exemptions must be made on the basis of proven safety based on experimental data (ie. no significant risk.)

3. The list of exchangers should be by species, not genus, and added only on the basis of safety as well as exchange.

4. There should be full compliance with NEPA, and adequate opportunity for public comment.

Exceptions

The guidelines point out that weight must be given to both "scientific and societal benefits and potential risks," acknowledging that these decisions are not only technical, but are political. This situation demands much broader representation in the decision-making. Appropriate notice and comment is simply not adequate; the decision is already made. The decision makers can and do ignore public comment.

Exceptions are easements of prohibitions. These experiments were not prohibited lightly; the ban should not be lifted without careful consideration of all possible consequences drawing on the full range of expertise, as well as the public.

Recommendations:

1. All exceptions from the guidelines should be undertaken only after a full environmental impact statement to allow for assessment as well as better public input and awareness. In the case of a single risk assessment experiment where containment will not be breached, an EIA may be satisfactory.

2. Waiver on large scale culture size should only be granted after full scale risk assessment studies on the organism, and an EIS on the large scale production process have been done.

3. The guidelines presently state that prohibition of deliberate release into the environment should only be lifted only "if the requirements for a waiver are met, and if the requirements of NEPA are considered." What are these requirements for a waiver? And aren't the requirements of NEPA going to be met, not only considered?

Certification of Host-Vector Systems

New host-vector systems raise a whole new range of ecological and biological issues. The projections of safety being made from e. coli k-12 are no longer germane. These decisions must be made on the basis of as complete knowledge as possible. The NEPA process will help to inform the decisions.

Recommendation:

1. Full compliance with NEPA must be required before approval of any host-vector system, as well as early public notice and

opportuntiy for input before the decisions are made.

III. Responsibilities of the NIH

Due Process Considerations

1. The reference to "shifting the burden of proof" should be stricken from the guidelines. As discussed earlier, it is clearly premature. For an excellent discussion of where the burden of proof lies, refer to Peter Hutt's letter (March 3, 1978) to Dr. Fredrickson, p. 2.

2. "Appropriate notice and opportunity for public comment" is an inadequate public participation mechanism. By that point, the important decisions have already been made. Our comments in the past have too often been ignored. For example, one commentator at the Director's Advisory Committee (DAC) meeting in December did an extended critique of the probability analysis used to justify the safety of recombinant DNA research, particularly pointing out the fallacies in the work of Robin Holliday. Holliday relied on fault tree analysis, the use of which was initially discredited during the space program, and more recently widely criticized in the Rasmussen report. Nevertheless, Dr. Fredrickson refers to his work as "noteworthy" and makes no mention of the critique delivered before him in December.

The public perspective must be introduced at a much earlier stage in the decision-making.

3. In that regard, the Director's Advisory Committee (DAC) does not adequately substitute for public involvement on the Recombinant DNA Advisory Committee (RAC). Once again the decisions are made by the time the "public" gets input. It may be possible to change the details, but the basics are set in concrete. It is this kind of public participation that has led to distrust of the policies of the NIH.

4. Public membership must be substantially increased on the RAC. As the Stevenson subcommittee concluded, "the technical and social policy aspects of even physical and biological containment standards or host-vector approval cannot be readily distinguished." Scientific decisions cannot and should not be separated from their social and political context. In attempting to do so, the NIH has insured that the decisions were simply made in a less representative social and political context.

Recombinant DNA Advisory Committee

The RAC has turned out to be much less conservative than the Director, NIH. In many cases, they went further in the PRG-RAC than the Director finally allowed in the PRG-NIH. Advisory Committees have often been expected to counter balance internal conflicts of interest, and in this case ensure that the public health and safety is being considered adequately. Unfortunately, the RAC does not seem to be fulfilling that function.

Recommendations:

1. EPA, OSHA, FDA, and CEQ should have full voting membership on the RAC. This is essential now that the NIH is accepting voluntary compliance by industry. In order to protect proprietary information, the RAC will have to hold meetings not open to the public. We need to have some assurance that our concerns will be represented. Perhaps more importantly, the RAC could use the advice of experienced regulators, particularly as they begin to deal with industry.

The Interagency Committee is not adequate participation and input for these agencies. It has not met once this year. The advice of EPA and OSHA, in particular, will always be "appropriate" (p. 33051), they should be fully involved in the decision-making.

2. The majority of the open spaces on the RAC should be filled with individuals nominated directly from the public. Until we have members who share our perspective, and whose judgement we trust, the decisions of the RAC will always be suspect. This trust is in the long-term interests of the NIH, as well as ourselves.

Penalties

HEW must find some credible mechanism for ensuring enforcement of the guidelines; withdrawal of NIH funding is totally inadequate The sanction is so severe that the NIH will probably never use it, except for the most gross violations, witness the recent experience with UCSF and Harvard.

HEW must find some mechanism by which penalties can be assessed appropriate to the infraction, an then use them as required.

IV. Responsibilities of the Institution

Health Monitoring

Institutions are only required to determine the necessity of doing health monitoring, not to actually do it. There is nothing in the guidelines that requires medical monitoring, data collection, maintenance of records, or most importantly good experiments designed to determine what if anything is happening with recombinant organisms inside human bodies.

Very little study has been done on the epidemiology of recombinants in humans. And although we've heard repeatedly that no one has been injured by this kind of research, they're still saying that about commercial nuclear reactors. It is important to note that the most dangerous kinds of experiments have not been done. Almost all the work has been executed with the safer recombinants, primarily because of the lack of high containment labs. But with the new guidelines, what used to be done in P-4 and P-3, can now go on in P-3 and P-2. New host-vector systems, work in wild-type e. coli now allowed through exemption, and large scale processes will make what little we know essentially inapplicable.

Recommendations:

1. Requirements for data collection and record-keeping in a unified manner should be mandatory. This will obviously allow for easier accumulation and analysis.

2. Encourage and support epidemiological studies of recombinant DNA laboratories to develop the information needed to make decisions on the basis of experimental data.

3. Carry out an assessment in a year or two to see if a centralized collection of this data is required.

Institutional Biohazard Committees

The NIH has delegated considerable authority to the institutional biohazards committees (IBC):

1. to allow research to proceed prior to NIH approval on changes in P-1 through P-3 protocols.

    a. This policy will lead to confusion and discrepancies between institutions. Approximately 10-15% of all MUAs are disapproved by the NIH on non-trivial grounds. This creates ample opportunity for problems. Recent conversations with ORDA indicate that processing of MUAs is down to 24-48 hours.

Recommendation: Require NIH approval on non-trivial changes on P-2 through P-4. If significant delays develop, hire more staff; fund less research. (one staff person worth)

2. to approve for single step reductions in containment levels for experiments with purified DNA and characterized clones.

    a. authority for single step reductions in containment levels, as well as the previous provision, will lead to a patchwork of local regulation which was decried by the scientific community in regards to federal preemption of stricter standards, but is apparently welcomed for lowering them. Furthermore, there is no requirement that these fully "characterized clones or purified DNA" be safer.

Recommendation: Prior approval by the NIH should be required on P-2 through P-4 protocols and only granted on the basis of proven safety (ie. no significant risk). The function of the insert as well as its quantitative purity should be taken into account.

3. to "review and oversee" all recombinant DNA projects because of the "impossibility of Federal surveillance to enforce these standards externally, and because it is an "effective and relatively inexpensive administrative mechanism."

    a. It is the above sections which underlies the basis for our concern about the whole regulatory approach that the NIH has developed. The last year has shown that

> local as well as Federal surveillance has been inadequate to enforce these guidelines. As chairman of the Harvard Biohazard Committee, Bernard N. Fields has pointed out in the Boston Globe, "Monitoring of compliance is on an honor system." That is hardly an "effective administrative mechanism."

The proposed revision requiring one public member and recommending one non-doctoral staff person, chosen by the institution, is absolutely inadequate to ensure a balancing of perspectives. One public member on a committee of 9-15 will be intimidated, ignored, and outvoted continually.

Recommendations:

1. One third of the members of an IBC should represent the public and worker interests. The use of institutional scientists and environmental health and safety personnel as technical consultants has already been discussed in the Laboratory Monograph. This lessens the need to have the overwhelming percentage of the committee representing scientific expertise. The make-up and selection process should be specified in great detail in the guidelines. For example:

> One or more non-doctoral staff nominated by that population of workers.
>
> One or more "volunteer" representatives well-suited to represent the public interest.
>
> One public health official and/or elected official.

The public member should volunteer to ensure continuing interest and effectiveness. Notification of openings should be made in local media. Selection should be made by the local governing body or health department.

2. One third of the members should represent scientific disciplines related to risk assessment (e.g. epidemiologists, environmental health scientists, physicians with both research and clinical experience in infectious disease, microbial ecologists.

3. One third should represent disciplines relevant to recombinant DNA technology, biological safety, and engineering.

4. The IBC must have all meetings publicized and open to the public except for those portions specifically dealing with confidential information. This should be required in the guidelines.

Conclusion

Until there is adequate representation of diverse interests on the decision-making bodies, oversight and regulation of recombinant DNA research is a sham. The present proposed revisions do not adequately protect the public, the worker, and in the final analysis, the recombinant DNA researcher himself.

TESTIMONY PRESENTED TO THE
HEW HEARINGS ON THE
PROPOSED REVISED GUIDELINES

September 15, 1978

My name is Thomas Blessing. I presently serve as the Drain Commissioner for Washtenaw County, Michigan. The position is a county-wide elected position serving a population of 260,000. Prior to involvement in the public policy questions of my present position, I gained detailed experience in air handling equipment as head of Research and Planning of the City of St. Paul's Air Pollution Control Agency. If one couples this experience with my work as a Research Assistant in a laboratory studying photo-synthetic bacteria, I believe I can offer a unique perspective to the public policy questions that arise from recombinant DNA research.

I intend to discuss primarily the policy questions. Others will be addressing the technical problems with the revisions. I must state at the outset that, quite clearly, the decision-making on this issue has been dominated by a scientific community enamoured with visions of new discoveries and exciting breakthroughs. An I am not surprised. Many of these visions may be fulfilled. Recombinant DNA research technology is a powerful biological tool. And the NIH has responded to this enthusiasm and not responded to statements calling for caution.

Statements throughout the introduction refer to "overwhelming sentiment" (p. 33043), "growing sentiment" (p. 33044) and "general endorsement" (p. 33051). This seems to be used as the justification for initiating the relaxation of standards. The fact that this "sentiment" and "endorsement" consists almost exclusively of those with a vested interest in rapid, unfettered research is conveniently set aside. The policy questions and social risks of a tool as powerful as recombinant DNA research are simply being ignored by the present decision-makers.

The result is a set of guidelines that do not reflect the kinds of concerns such decisions properly require.

For example, on p. 33043 of Federal Register Volume 43, Number 146, the statement:

> "... There was overwhelming sentiment for exempting from the Guidelines experiments involving recombination of DNA within the same strains or from pairs of organisms that transfer genes in nature."

Also, p. 33051 addresses the question of the public's role in the exemption process by stating, in part:

> "the membership of the RAC will be broadened modestly as needed for expertise, but provisions for public notice and opportunity to comment ... can be used to ensure adequate public input when the issues warrant."

The revised guidelines implement this pholosophy with under language found in Part IE4, E5 and Part IVB1d.

The underpinning for these rules is the assumption that if it occurs in nature it is okay. This totally ignores the question of rate of recombination under forced laboratory conditions.

The parallel and equally fallacious arguement is, "Because nuclear fission occurs naturally on earth, regulation of experimentation can be minimal and exempted by an appointed Washington official."

Whomever in NIH is accepting the proposed exemption criteria is adopting a simplistic notion of reality.

In general, NIH is seeking to relax the safeguards imposed on various experiments. Physical containment is not the fail-safe system you are being led to believe.

While in St. Paul, I personally inspected the air handling equipment of more firms and manufacturers than most people will see in a lifetime. While taking courses in environmental micro-biology, I studied and

performed the sampling for micro-organisms in hospitals and their so-called "clean rooms". And all these systems would fail on occassion. No exceptions.

When technologists have been asked to selfregulate, the track record is poor.

Science News reports in its September 9, 1978 issue that a new case of smallpox has been contracted by a photographer in the Birmingham University Hospital Medical School in England. The virus was being stored one floor above his work area. I don't know what safeguards were being taken. However, I am sure that the laboratory involved presumed them adequate. This is one example.

And NIH is proposing to relax safeguards and limit the decision-making of exemptions to a group that lacks a general public policy perspective.

This is not acceptable.

I have touched on a small fraction of the problems with the guidelines. I have spoken of the problems with the exemptions and with the basic decision-making structure of the guidelines.

I ask that you re-draft the guidelines to reflect these concerns.

Testimony: Christine Oliver, MD, MPH for the Oil, Chemical and Atomic Workers International Union

Hearings on the NIH Proposed Revised Guidelines for Recombinant DNA Research
Department of Health, Education and Welfare
Review Committee

September 15, 1978

My name is Christine Oliver. I am a physician, board certified in internal medicine and a Clinical Associate in the Department of Medicine at the Massachusetts General Hospital in Boston, Massachusetts. I have a Master of Public Health Degree in Occupational Health from the Harvard School of Public Health.

I am currently working with the Oil, Chemical and Atomic Workers International Union (OCAWIU). I am speaking today as a representative of the Union and for the Union.

I will address today the issue of recombinant DNA research as a threat to the collective and individual health of the potentially exposed worker, and the Proposed Revised NIH Guidelines as they relate to that threat. I will attempt to put the issue into perspective by discussing briefly the health and safety situation as it currently exists in many work environments.

During the past eight weeks I visited five industrial plants whose workers are members of the OCAW to assess the health hazards. These plants included chemical plants in New Jersey and Louisiana; oil refineries in Louisiana; a pesticide plant in Tennessee; and a chemical-pesticide plant in Illinois. Each employs at least 150 production workers. Each is subject to OSHA regulations. In each plant the workers are represented by a strong health-oriented Union.

What I found in each plant was an abysmal failure to abide by OSHA regulations and the dictates of human conscience to provide for the worker a safe and healthful work place. The following are examples:

1. With two exceptions, each company refused to furnish the workers with a list of the generic names of all the chemicals to which they are exposed. And in the cases of the exceptions, no data on chronic toxicity -- such as cancer of the lung, cancer of the liver and delayed neurotoxicity -- was supplied.

2. There was at best sporadic environmental and biological monitoring for exposure to known carcinogens and respiratory and nervous system toxins. And there was a failure to inform workers of the results of this monitoring.

3. There was no ongoing collection and analysis of relevant morbidity and mortality data.

4. There was inadequate to nonexistent labelling of vessels and pipes containing toxic and carcinogenic substances.

5. Local and general exhaust systems were poorly functioning to nonexistent.

6. And finally, many of the workers were experiencing adverse health effects as a result of hazardous exposures. In one chemical plant, for example, 90 of 125 workers had abnormal liver function tests.

These situations exist despite the fact that worker exposures are to chemicals whose effects are at least reasonably predictable and in some cases reversible; despite the fact that both environmental and relevant biological monitoring techniques are available; despite the fact OSHA regulations are applicable; and despite the fact that workers are represented by a strong union. In contrast is the situation that exists with regard to worker exposure to recombinant DNA molecules:

1. The nature and reversibility of the effects of worker exposure to recombinant DNA molecules are unknown and in many cases unpredictable. And in fact, the effects of exposure to the attenuated organisms containing the recombinant DNA material are unknown. For example, a prospective study of the ability of the "benign" E. coli K 12 to colonize the urinary tract of exposed laboratory workers has not been done. And yet, E. coli is responsible for 70 to 80% of urinary tract infections, and such infections afflict 5% of a general medical clinic population. Urinary tract infections are a major source of bacterenrias, which kill 66,000 to 165,000 persons each year.

2. Since the effects are not known, accurate biological monitoring is impossible. Latency periods are unknown and unpredictable. Thus establishment of cause and effect and ultimate prevention of permanent adverse effects are impossible.

3. Adequate techniques for environmental monitoring for recombinant DNA molecules do not exist. So that with neither accurate biological monitoring nor adequate environmental monitoring, the ascertainment of the level of worker exposure to recombinant DNA material is impossible.

4. Contrary to the statement in the July 28, 1978 Federal Register (p. 33065) that "OSHA standards and procedures apply to most institutions," OSHA regulations do not apply to University and Federal research laboratories, where much of the recombinant DNA research is being done.

Thus many of the workers who face hazardous and unpredictable exposures to recombinant DNA molecules are not protected by OSHA. And they are not protected under the proposed Revised NIH Guidelines.

1. The "Guidelines" are simply guidelines. They do not have the force of law behind them. They provide for sanctions that are inadequate to ensure compliance. To wit: (p. 33087, IV-D-1-(a), "noncompliance may result in suspension, limitation or termination of financial assistance for such projects...."

2. The Guidelines do not apply to industry. To compound this error of omission is the notorious problem in industrial research of large scale production. And as commercial use increases; production will increase; job speed-up will result; accidents will increase; and hazardous exposures will increase.

3. The Guidelines are inadequate in their specification for biological monitoring or medical surveillance: (p. 33084, IV-A-1-(c)). The institution would be given responsibility for the determination "in connection with each project, the necessity for medical surveillance of recombinant DNA research personnel." Thus,

    a. The institution may determine that medical surveillance is unnecessary.

    b. The stipulation is for "research personnel" only. It ignores maintenance and janitorial staff, and the families of exposed workers.

    c. The requirements are too nonspecific and leave too much to the discretion of the individual institution.

4. The Guidelines are inadequate in their requirements for worker education regarding the hazards of recombinant DNA molecules. They state simply (a) (p. 33053), that the NIH has a contract...to develop "minimum standards for training participants in recombinant DNA research;" and (b) (p. 33085, IV-A-4-m-(1)), that the principal investigator shall "make available to the laboratory staff copies of the approved protocols that describe the potential biohazards and the precautions to be taken." Both provisions ignore other than research personnel who are exposed. Any my experience with industrial training programs and provision of data sheets is that they are inadequate and incomplete.

5. The Guidelines place primary responsibility (p. 33085, IV-A-2-a-c) for key technical and procedural decisions in the hands of the Institutional Biosafety Committee: to approve recombinant DNA research projects; to approve reduction in containment levels; to monitor compliance with the Guidelines; and to review and approve emergency plans covering accidental spills.

   This situation is analogous to the allocation to the states of responsibility for monitoring and enforcing industrial compliance with OSHA standards. Such a scheme has proved to be disastrous for Labor because of local conflicts of interest and incompetence.

Given the unknown nature of the effects of exposure to recombinant DNA material, and the failure (and in fact, inability, given the current state of knowledge) to provide a mechanism for the adequate protection of the worker, the risks of recombinant DNA/research would seem to far outweigh the benefits.

And what are the benefits? The postulated benefits of recombinant DNA research include the correction of genetic defects; the prevention of cancer; the treatment and possible prevention of diabetes; the prevention of heart disease; and the satisfaction of the world's nutritional needs. But other less hazardous, less expensive and more readily available means to the same ends exist.

1. Identifiable genetic defects afflict a small percentage of the U.S. population. Genetic counselling and amniccentesis exist as preventive measures.

2. Seventy to 90% of cancer is environmentally induced. Of these cancers at least 40% are occupationally induced. Elimination of toxic exposures at the workplace; change in dietary and smoking habits; reduction in air and water pollution; and routine screening procedures

such as proctoscopy, Pap smear and self breast exam exist as preventive measures.

3. The majority of diabetes is adult onset, and potentially preventible by a lifetime of good dietary habits. Juvenile onset diabetes is possibly preventible by vaccination against viruses thought to precipitate the disease in certain vulnerable individuals. And insulin is available in sufficient quantitites to treat juvenile and recalcitrant adult onset diabetics.

4. Risk factors for heart disease have been identified. These risk factors can be significantly reduced, if not eliminated, by alteration in dietary and smoking habits; by aerobic exercise; and by reduction of certain types of work related stress.

5. Meeting of the world's nutritional needs is not a matter of increasing food production but rather of a more efficient and equitable distribution of food that is already being produced.

In summary, the adverse health effects of exposure to recombinant DNA material are unknown and, in some cases where predictable, irreversible. To adequately protect the worker from exposure to recombinant DNA material is impossible. The Guidelines have limited applicability; they are nonspecific in such important areas as medical surveillance and emergency spills; and they lack adequate sanctions. Accidents are inevitable and in fact have already occurred. There are other less hazardous means of achieving the same ends.

To promulgate such a set of Guidelines that is neither enforceable nor adequate nor applicable to all recombinant DNA research is an unconscionable act that only serves to create a false and dangerous sense of security. Therefore, the Oil, Chemical and Atomic Workers International Union, in order to protect the present and future health of this country -- both the Worker health and the Public health -- has no choice but to call for a moratorium on all recombinant DNA research.

Testimony Presented at

NIH Hearings

on

Recombinant DNA Guidelines

by

Carl Kline

Western Maryland

Clergy and Laity Concerned

September 15, 1978

My name is Carl Kline. I am here representing Western Maryland Clergy and Laity Concerned. Clergy and Laity Concerned is a national religious organization concerned about issues of peace and social justice. The Western Maryland chapter is centered in Frederick, Maryland. Frederick's renown began with the lyrics of Francis Scott Key and the courage of Barbara Fritchie, took a more infamous turn as the biological warfare center of the country, and now waits with hope and dread the new national center for recombinant DNA research. Decisions made as a result of this hearing may well affect Frederick more seriously than any other locality. And that brings me to the first reason for this testimony, as a citizen of the Frederick area.

The nature of this hearing and the decision-making process of the National Institutes of Health betray an incredibly serious bias against the democratic process. It has been clear since Frederick was announced as the future location of the new facility that the decision had been made by a federal governmental-scientific elite, that any community concern or questioning could eventually be met by patience, pay-rolls and good P.R. It has been one more example of government pursuing its own interest, to the exclusion of the larger public it was designed to serve. I am here to suggest today that the prior question still remains. Should recombinant DNA research be conducted in Frederick, Maryland at all? Through what process has the public given its authorization or pledge of support?

The National Institutes of Health has a responsibility, especially in matters of complexity and controversy, to be an educative organ; to encourage debate; to support the airing of diverse opinions; to initiate public discussion and resolution; to help raise with the average citizen the far-reaching value questions involved. Cumber-

some? Perhaps. But if governmental agencies will not assume some such responsibility we should not be surprised at democracy on its death bed. Should the NIH guidelines be modified? When, and in what manner, will the citizens of Frederick be asked that question? My assumption, based on past history is, this is their only chance. In my mind, that is socially irresponsible.

The second reason for this testimony is more specifically related to the broader issue of the hearing, whether safety concerns can be modified and revised guidelines adopted.

National Clergy and Laity Concerned has been focusing on concerns of Human Security. Most of that concern has been with the nuclear arms race and the threat posed by an increasingly radioactive environment. Our chapter in Western Maryland has added to that concern the biological revolution, and the dangers posed to humankind by genetic research.

We have concluded that the technical discussions about facility classification, and all the steps taken to insure containment, are of great immediate importance and the present guidelines should be continued; but that ultimately the discussions, kinds of facility and guidelines are simply irrelevant. They are probably most helpful in relieving the conscience of the technicians, but most unlikely, over time, to prevent serious threats to human security. Already, recombinant products, threats to human security included, are becoming the responsibility of other government agencies like FDA and EPA (with less than spotless records), and those who do the research move farther and farther from accepting responsibility for the products.

Now perhaps we would have a more optimistic view of the future if our roots were elsewhere or our immediate experience were

different. But as members of Clergy and Laity Concerned we are rooted in a faith that proclaims a Creator, a God of all Life and Being, and our human security lies there; not with a laboratory technician, or effecient administrative officers, or comprehensive offices of security and safety. And that you not misunderstand me, we also have greater faith in the process of evolution and the pace at which life evolves, than we have in a scientists' genetic intervention or an NIH time-line.

Also, our immediate experience suggests to us that our faith is not blind faith. There are serious reasons why we choose to place our confidence elsewhere. There is history shaping our concerns.

We received significant promises with the arrival of the nuclear age. Benefits seemed to outweigh costs. Now we are forced to coin new words like John Somerville's "omnicide," killer of all, for the nuclear reality we face daily. And we received significant promises with the arrival of the chemical revolution. Benefits seemed to outweigh dangers. Now we are forced to coin words like ecocide, killer of the ecosystem, for the carcinogenic pollution that ravages the planet. Again, now, we are assured of important benefits, with minimal dangers, by the biological revolutionaries. And we will most likely be forced to consider genecide, spelled in a new way, with an "e" not an "o."

Assuredly, natural recombination occurs, without our intervention. Assuredly, natural recombination is a moving force in the evolutionary process, in about 1% of the cases. Where violent intervention in genetic heritage occurs in the natural process, 99% of the time it is harmful or detrimental to the organism involved. The most dangerous research begins, in our opinion, when we are most convinced that we can secure our own genetic

future; when we are convinced beyond a shadow of a doubt that we really know what we are doing; when we begin to exhibit the age-old attitude of arrogance. The subject of this hearing convinces us that the biological-technological imperative moves us quickly toward genecide.

If nothing else, this testimony is presented in the hope that as people focus on issues of human security, a minimal degree of humility be present; acts of God might be recognized as something other than acts of man, blamed on God; and that if we are honest with ourselves and others we must eventually confess that we always end up knowing less than when we started.

Finally the directions and dimensions of the biological revolution developing from this new technology, a technology that will most likely become common-place, soon, are leading some of us in the Christian community to oppose it totally. We are being blinded to any distinctions in kinds of research by what seem to us to be misinformed and mistaken assumptions underlying the work; and by the enormous potential for death and destruction (especially biological warfare) implicit in the work.

We are convinced that ultimate value lies in "life itself;" all of it is "good;" not simply life that is "human;" and we are not advancing if we increase the quality of human life and further threaten life itself. Deeper perhaps than that, as we move closer to genetic engineering, we are convinced there is something irreparably human about human genetic mistakes. Already, if diabetics have reason for hope, dwarfs beware.

In closing, I agree with Gordon Cosby that it isn't our MAD (mutual assured destruction) nuclear policy that has kept humankind from nuclear annihilation. "Ultimately we are still here by

the grace of a compassionate God and the work of some serious peacemakers. As we enter the genetic age, one could hope that decision makers would worry about human security from the effects of individual and corporate greed, individual and corporate ignorance, individual and corporate power and individual and corporate pride; as they worry about bricks and mortar, air vents and air flows, biological and physical containment. And that barring omnicide, my children would not be faced with genecide.

Statement at HEW Public Hearing on Recombinant DNA Guidelines Revisions

Barbara H. Rosenberg, Ph D, Associate Member, Sloan-Kettering Institute and
Associate Professor, Biochemistry, Cornell Univ. Medical College

Grace Ungers, M.S.,Research Assistant, Sloan-Kettering Institute

The use of Recombinant DNA could potentially alter man and his environment, for better or worse, by intention or accidentally. Therein lies both the promise and the danger of this new technology.

The NIH Recombinant DNA Advisory Committee and the guidelines were set up to minimize the hazards that might arise accidentally from various small-scale experimental procedures envisaged in current biological research, mainly academic research. It was academic research that gave birth to Recombinant DNA techniques; and the academic research community, primarily under the aegis of the NIH, has been the first to exploit the techniques as well as to recognize their possible risks. But the recent syntheses of somatostatin and insulin and the rapid emergence of industrial interest show that academic research will not have the field to itself for much longer. New problems are about to arise, resulting from the near impossibility of preventing the escape of recombinant organisms when they are produced on a large scale for drug manufacture; problems also that may result fro. of predicting all the environmental consequences, the intentional release of large quantities of genetically-engineered organisms such as oil-eating bacteria or nitrogen-fixing plants. But the regulation of industrial applications is outside the scope of the NIH, and evaluation of the public stakes in the application of this new technology is beyond the competence of the research biologists who make up most of the membership of the advisory committee. Societal priorities, ethical questions, and nonscientific judgements are going to be involved, and if the authority is not broadened and the decisions are not very soon delegated to a more qualified and representative body, they are going to be made, de facto, by commercial interests alone. Experience shows that commercial decisions have a way of becoming economic necessities that are independent of their intrinsic value - witness the difficulties of phasing out the manufacture and use of carcinogenic insecticides like Mirex and chlordane or of nitrite

in bacon. Nonetheless, once an unforseen hazard is identified in these technologies, they can, in principle, be halted. Not so with recombinant DNA technology. Once a dangerous recombinant escapes and finds an ecological niche, it is likely to be impossible to eradicate.

We therefore recommend that not just basic research but also industrial and other applications involving recombinant DNA should be universally regulated with the force of law, in the public interest.

Turning to the proposed revisions in the NIH guidelines, we would like to point out not only that some of them are potentially dangerous and unwarranted, but that they have been arrived at by unscientific methods that would never be judged acceptable for the establishment of even the most insignificant scientific facts. They are therefore all the more unsuitable for the establishment of scientific procedures where the public safety is concerned. After illustrating the unscientific basis for some of the revisions, we will return to the question of how to rectify the problem

Firstly, a great deal of weight has been placed on semi-authorized reports of discussions held at closed scientific meetings, attended by a small number of selected participants. The outcome of these meetings, in general, appears to represent the "best guesses" of those present, most of whom were interested parties. The proceedings of the meetings were not published for the inspection and criticism of the entire scientific community before they were accepted as a basis for lowering safety precautions. In normal scientific practice, meetings and discussions of this kind are considered appropriate only as a basis for choosing the more promising concepts for future experimental investigation. Most scientists can think back to discussions of this kind where the consensus later turned out to be dead wrong.

However, the Falmouth conference of last year has been used as the basis for downgrading the containment requirements for cloning foreign DNA in E. coli. This revision has been proposed without waiting for the results of experiments now in progress, designed under contract to the NIH to test an assumption on which the revision is based: namely, that the EK1 and EK2 strains of E. coli cannot escape from the laboratory by the usual routes. Recently, unexpected results have shown that the EK2 strain can survive spillage much better than had been anticipated. This indicates that caution is still in order, at least until the full results of the study become available in a year or so. It seems to us appropriate that the scientific data on this safety question be evaluated before rather than after giving hundreds of laboratories around the country the go-ahead to lower their precautions.

Another closed meeting, held at Ascot this year, serves as the ostensible basis for the drastic downgrading of containment requirements for recombinants involving animal virus DNA, including tumor viruses. Actually the conference reportedly recommended P2 containment, but an American subgroup subsequently met and opted for P1 and EK1. Now just as an aside, let no one suppose that P1 actually represents "containment." P1 and even P2 levels of precaution may prevent massive accidents but they simply cannot prevent ultimate escape from the laboratory. An experiment bearing on the safety of escaped viral recombinant DNA has already been carried out - the Rowe-Martin risk assessment experiment with Polyoma DNA. ——>

<—— Somehow the results have never been published, but they are reported to show that a recombinant plasmid carrying viral DNA can be infectious in mammals. Thus, the insertion of such recombinant plasmids into E. coli gives the virus an entirely new route of attack which could be dangerous even if the coli itself did not survive after entering the animal or man. The new route might even prove to be more efficacious than the normal mode of infection by the virus.

It is therefore not correct to assume that recombinants containing virus must be less dangerous than the virus itself. Experimentation on the extent of the hazard posed by creating a new vector for cancer viruses is surely called for before this type of work is permitted at all, much less under the almost totally permissive conditions proposed.

A similar argument applies in the case of the bacterial types which are proposed to be exempted from the guidelines. Among these are some species which are plant pathogens, and some of these have never been proven to exchange genetic material naturally with certain other organisms on the list. Recombination could give the pathogens a new ecological distribution and the ability to infect new plant populations. For these reasons, recombinants are potentially more dangerous than the natural pathogen itself. It seems to us that exemption from the guidelines can only be justified by firm evidence for widespread natural genetic exchange between the specific species to be recombined; but this evidence is not available in all the cases to be exempted. Moreover, the Recombinant DNA Advisory Committee has recently decided that data on genetic exchange, to be used as the basis for exempting organisms from the guidelines, need not even be published in refereed scientific journals! Thus the data need never be subjected to examination or criticism by others with perhaps greater knowledge of the systems under study; conflicting data need never come to light. A very fundamental scientific control involving peer review has been sidestepped. This goes to the very heart of the ethic of the scientific method.

In the case of shotgun experiments, containment reduction has been based on the unwarranted extrapolation of limited data. It is, to say the least, premature to conclude that all eukaryotic genes act through a messenger that cannot be processed in bacteria, and therefore cannot produce harmful products in bacteria. So far this has been shown for only a handful of genes, although there are a million or so in a human cell. More importantly, the genes that have shown this behavior are of necessity the ones that are easiest to study, and these are all of special types; they make proteins in quantity for export outside the cell, or they are in viruses with restrictively small genomes, etc. These special genes might require atypical controls and may therefore not be representative of all eukaryotic genes. We consider it scientifically irresponsible to jump to conclusions in this way for public relations purposes, when no reputable scientist would make such gross extrapolations in his own work.

A few misguided scientists have not hesitated to make it clear that they regard the guidelines as mere window-dressing to allay unfounded public fears. These people are certainly entitled to their opinions as to the safety of recombinant DNA technology, but since they are opinions rather than knowledge based on established fact, there is no reason why they should be taken any more seriously than the opinions of less interested parties with a claim to greater objectivity.

The fundamental problem with the guidelines and their revisions is that they have been entrusted to the NIH, the sponsor and promoter of progress in biological research (including recombinant DNA techniques), and to its Advisory Committee, which is composed largely of scientists working with recombinant DNA or in closely related fields. A conflict of interest is bound to occur, for it is only natural that these groups will appreciate

the potential value of the work they know so well and will feel consternation at any contraindications. It is not fair to ask the discoverers and developers of a powerful and exciting new technique to take the responsibility for regulating it also.

Just a word about local biohazards committees- In our experience they are largely under the control of the scientists working with the biohazards, and can therefore not be counted upon as a counteracting influence. Moreover, since the hazards (especially industrial ones) may not be localized, it is not right to give the local committee of Nutley, N.J. the power to make major decisions that might affect the welfare of New York City. Certainly the local committees should have the power to disapprove, but their approvals should be subject to a review at which uniform/minimum standards are applied across the country.

In sum, we would like to make the following recommendations: That the Secretary of HEW take control of recombinant DNA activities under Sec. 361 of the Public Health Service Act or similar existing authorization; that his control extend to all recombinant DNA activities in this country, including those not supported by the NIH or other government agencies; and that he set up an Advisory Committee including representatives from other relevant agencies such as EPA, OSHA, CDC, etc., as well as disinterested individuals in various fields relevant to the public interest. Some appropriate fields for the members of such a committee have been listed in the Senate Joint Resolution No. 71, presented by Mr. Mondale in March, 1973, and in the recent bill HR7897. Nominations for committee membership should be solicited from the public and from interested organizations, and the appointments should reflect a wide spectrum of viewpoints. The Advisory Committee, with the help of technical subcommittees appointed by the committee as needed, should 1) review and revise the guidelines in the future; 2) review and approve or disapprove all proposed recombinant DNA projects that have been approved by local committees; 3) review and make recommendations to the Secretary concerning proposed exemptions from the guidelines, reductions in containment, or other waivers; 4) make a study of proposed industrial applications and proposed operations involving deliberate release of recombinant organisms into the environment, in order to determine whether there is sufficient hard scientific data on which to base a meaningful risk/benefit analysis in the public interest; and 5) the committee should see that such an analysis is carried out before authorization of such activities, or it should propose further risk assessment experimentation or the development of new safety measures or the acquisition of additional basic information, when these are deemed necessary for adequate judgment of a proposed recombinant DNA activity. Public

hearings should be held in conjunction with all major decisions.

The working of a newly-constituted and more widely representative committee under the Secretary of HEW could be viewed as a trial or test system to determine whether existing laws and regulations are adequate, or whether additional Federal legislation will ultimately be needed -- and if so, what type of legislation could best insure that the public interest is not overshadowed by the undoubtedly important but subsidiary claims of biological research and its commercial application. If legislation is required, there is clearly no consensus at present as to its form; the present self-regulation under the NIH has only served to polarize opinions and to cut off bonafide exchange of ideas. A new experiment is called for. Even if it should prove to be a temporary expedient, it will provide much-needed new data on which to base future decisions.

Testimony before the HEW Committee reviewing proposed revised guidelines

for recombinant DNA research.

September 15, 1978

Daniel Nathans, M.D., Professor and Director, Department of Microbiology,
Johns Hopkins University, School of Medicine, Baltimore, Md.

For the record I want to summarize my scientific background and interests in relation to this testimony. I was educated in medicine, specializing in internal medicine, and subsequently went into molecular biology and microbiology. For the past 16 years I have taught medical microbiology to students of medicine at Johns Hopkins. My research, supported by the National Cancer Institute and the Whitehall Foundation, has centered on the molecular biology of tumor viruses. Part of my research involves recombinant DNA methods to study aspects of tumor virus interactions with cells. I was a member of the committee that in 1973 called for NIH guidelines for recombinant DNA research, and earlier this year, I served on the committee that recommended changes in the guidelines dealing with viruses.

The main point of my testimony is that the proposed revisions of the guidelines are justifiable on the basis of recent experience with recombinant DNA and a rational re-consideration of potential hazards of microorganisms containing recombinant DNA. I also believe that the revisions will allow a more natural and creative development of research in those many areas of biology and medicine to which recombinant DNA methods are applicable, resulting in advances that would not occur under the present guidelines.

I need not recite the experience with recombinant DNA over the past four years. On the one hand, the great promise of the methodology is being realized; and on the other, no single instance of harmful effect has been reported. During these years also additonal instances of natural interspecies recombination of DNA between microbes, or between viruses and cells, have been described that make it appear that such genetic interchange is widespread in nature. Therefore, there is now less concern both about the imminent "escape" of an artificial pathogen and about the novelty of microbes carrying genes from distant species.

The rest of what I have to say bears on a rational re-consideration of potential hazards of recombinant DNA research. By "rational", I mean related to prior experience. I think we have had available relevant experience with microbes that was not well utilized in the development of the current guidelines, but is reflected in the proposed revisions. For example, the experimental evidence that non-pathogenic bacteria like E. coli K12 are not converted into contagious pathogens by acquiring small clusters of additional genes, even from donor pathogenic strains, has been emphasized by medical microbiologists meeting at Falmouth. We have had long experience in the safe handling of pathogenic microbes. In most cases simple microbiological methods suffice. For instance in our medical microbiology course, students work with cultures of Neisseria meningitidis, a cause of meningitis; Shigella dysenteriae, the cause of dysentery; Salmonella typhi, the cause of typhoid fever; and many other real pathogens. Over a 16 year period I have not been aware of a single case of disease related to these laboratory exercises, in spite of periodic spills and obvious infection. This experience also illustrates the well-known fact that so-called "escape" of microbes from the laboratory or infection of a laboratory worker is far from equivalent to disease production, let alone epidemic disease, which is almost unheard of as a result of laboratory infection. I would argue that a century of experience with safe handling of real pathogens should influence the requirements for handling non-pathogenic organisms containing foreign DNA, whose potential pathogenicity is entirely conjectural.

In regard to viruses, the proposed revisions are based on a similar principle, namely that as a rule conditions used to work with the virus itself are adequate to work with recombinants containing segments of the viral genome, or with defective virus vectors. It is difficult to imagine how E. coli K12 containing a segment of SV40 DNA could be more hazardous than the SV40 virion itself. Likewise, defective SV40 with a foreign segment of DNA is much less capable of spreading in a population than is intact SV40. Moreover, it is clear that each of the mammalian viruses proposed as a vector for recombinant DNA (polyoma, SV40, murine and human adenoviruses) readily recombines with host cell DNA to form a large variety of recombinant viruses. In other words, we appear to be exposed to shot-gun type viral recombinants all the time in our natural environment.

Finally, I would like to comment on the proposed role of local biosafety committees in monitoring recombinant DNA research. It has always made sense to me to make the institution responsible for its own recombinant DNA research activities, as it is for other microbiological research and for use of radioactive materials. At Johns Hopkins the biosafety committee is serious in purpose and effective; its authority is recognized by everyone. Therefore, I support the proposed increase in local responsibility. Since revised guidelines specify the composition of the biosafety committees (including non-scientists and at least one member from outside the institution) and require prompt communication to NIH of new proposals, infractions, etc., I believe there is sufficient monitoring of institutional compliance with the guidelines.

September 15, 1978

Proposed Revisions to the NIH Guidelines for Research on Recombinant DNA

Gentlemen:

I am a research scientist in the Biology Department of the Brookhaven National Laboratory. In 1970 I received a degree (Ph.D.) in Microbiology from Washington University, St. Louis. For the past eight years my research has been concerned with molecular aspects of the replication of two DNA tumor viruses, human adenovirus (type 2) and simian virus 40 (SV40), and hybrids between these two viruses. Adenovirus-SV40 hybrids have been classified by the NCI as moderate-risk tumor viruses, and studies utilizing these viruses require procedures and containment facilities similar to those specified in the present NIH recombinant DNA guidelines for P3 containment. My laboratory is a P3 containment laboratory and has been operated as such for the past three years. Although my actual experience with recombinant DNA has not been extensive, I have been involved with three projects over the past four years that have involved the cloning of specific DNA fragments or the use of recombinant DNAs. At present, however, I am not involved in any research involving recombinant DNA. About a year ago I organized a symposium held at the Brookhaven National Laboratory which considered the prospects for the introduction, retention, replication, and expresssion of foreign DNAs in eucaryotic cells. Many of the ideas, techniques, and results which were discussed at that symposium involved recombinant DNA technology.

The expertise of many different people was utilized in the development of the original NIH Guidelines for Recombinant DNA Research. In developing revisions to these guidelines the Recombinant DNA Advisory Committee (RAC) consulted many additional experts and took into account the experience of many different laboratories involved in recombinant DNA research. While the scope of my experience does not match the collective expertise of the RAC, I do believe that my background qualifies me to evaluate certain aspects of the proposed revisions. This background includes a knowledge of microbial technique, a knowledge of recombinant DNA procedures and physical containment procedures, and a concern for the safety of my fellow workers and for the community at large. I have read and studied both the present Guidelines and the proposed revisions. I have also read about and listened to many agruments both for and against the proposed Guidelines and the proposed revisions. I have considered to the best of my ability the potential risks and the potential benefits which might come from recombinant DNA research.

I believe that the proposed revisions to the NIH Guidelines for Recombinant DNA Research provide no substantial increase in risk to mankind or to his environment and that they do substantially facilitate worthwile research. Consequently, I urge the adoption of the proposed revisions.

Specifically, I would like to speak in favor of the proposed reduction in containment level for research involving recombinant DNAs containing eucaryotic virus genomes. The arguments supporting the reduction in containment level for this area of recombinant DNA research are well presented in the report of the "Ascot" meeting held January 27-29, 1978. Certainly the prohibitions against cloning virus genomes which are contained

in the present Guidelines resulted from insufficient knowledge and incomplete reasoning. It is indeed difficult to imagine how a cloned virus genome would be more dangerous than the original virus itself. Many of us worked for years with eucaryotic viruses in laboratory situations without special precautions and without apparent harm. While common sense dictates the use of good technique in the handling of all virus material, there is no apparent justification for continuing the ban on the cloning of virus genomes except where specific risks are indicated. Similar reasoning applies to the use of viruses as vectors for the introduction of foreign DNAs in eucaryotic cells. Clearly these techniques make possible or practical many experiments which promise to yield considerable information on the organization and regulation of gene expression in eucaryotic systems.

I have one basic criticism of both the present Guidelines and the proposed revisions. This criticism is not concerned with safety afforded to the public by the provisions contained within the Guidelines, but deals with the administration of the Guidelines. The present Guidelines were created by the NIH and ultimate responsibility for those Guidelines resides in the hands of the Director of the NIH. However, the NIH Guidelines effectively apply to all government-sponsored recombinant DNA research, not just to NIH-funded projects. For the Guidelines to be meaningful it is essential that they apply to all research, but in essence, the present Guidelines give the Director of NIH a monopoly on recombinant DNA research. I anticipate that recombinant DNA technology will become increasing important in non-health related research, in agriculture, in energy and in industry. Thus it would seem reasonable that the responsibilities for regulating recombinant DNA

research should fall also on these other interests (e.g. NSF, DOE, USDA). I would suggest that this could be practically accomplished by investing more authority in the Recombinant DNA Advisory Committee and making that committee responsible to a committee of appropriate interested agencies.

Indeed, the NIH has done a remarkably good job of handling the recombinant DNA issue. However, I believe that it is a strength of American science that there are multiple interests and multiple resources to fund scientific endeavors. I should not like to see this option eliminated or diminished by restricting the authority for regulating a technique with broad potential applicability.

Gentlemen, I thank you for your interest and patience.

Dr. Carl W. Anderson
Associate Scientist
Biology Department
Brookhaven National Laboratory
Upton, New York

Testimony for HEW/NIH Public Hearings on Revised Guidelines for Recombinant DNA Research

September 15, 1978

Nancy Pfund, Research Associate, Division of Health Services Research,
Stanford University School of Medicine, Stanford, California

The introductory comments to the revised NIH guidelines by Secretary Califano and Dr. Frederickson make specific mention of the need to examine and refine the mechanisms for implementing and enforcing regulatory requirements for recombinant DNA research. In my testimony, I will address this issue as it relates to the local regulatory unit, namely, the Institutional Biosafety Committee (IBC). First, I will comment on the importance of the IBC in shaping a representative and efficient regulatory policy. I will then discuss the results of some preliminary data we have obtained on a sample of 30 IBCs. Finally, I will outline some plans for further research designed to fill gaps in current knowledge about the structure and function of IBCs. This research is part of a larger project of which I am a member, entitled, "Medical Progress and the Public: Ethical Issues in Biomedical Innovation," funded largely through the National Science Foundation's Program on Ethics and Values in Science and Technology.

I. Introduction

The latest version of the NIH guidelines gives major regulatory responsibility and decision-making power to Institutional Biosafety Committees (IBCs). Earlier versions of the guidelines, in contrast, focused on the responsibility of the IBC to implement nationally determined regulatory requirements and to provide the office of rDNA Activities (ORDA) with the information necessary for making final decisions on research proposals. There has since been a conscious shift toward locating more of the decision-making power at the local institutional level (Revised Guidelines, pp. 33045,

column 2). Newly mandated activities, such as approving the initiation of proposed rDNA experiments, considering and acting upon requests for approval of single-step reductions in containment levels for experiments with purified DNA and characterized clones, and participating in the development of emergency plans for accidental spills and personnel contamination, represent significant scientific and social responsibilities. To fulfill these larger functions effectively, biosafety committees must be procedurally sound and broadly representative.

While the revised guidelines present a more explicit outline for IBC composition than did the original guidelines, the wording is still general enough to permit great variation in the structure, and hence in the function, of these committees. The present composition of IBCs -- the representation of groups such as rDNA scientists, scholars in other fields, health and safety personnel, workers, and members of the public, remains largely unknown. Yet such information is essential in assessing the current operation of IBCs and in improving their future function.

II. Findings from Preliminary Sample of Thirty IBCs

Data

Data for a preliminary analysis of the membership composition of thirty of the approximately 150 IBCs throughout the country were obtained from the Office of rDNA Activities (ORDA) by Michael Maniates and Pamela Lippe of Friends of the Earth, and Phillip Bereano, Professor in the Social Management of Technology Program at the University of Washington. These thirty IBCs were selected on the basis of available data; they are listed in Appendix A. They represent research institutions as well as public and private universities, including many of the institutions receiving the

largest NIH grants for rDNA research (e.g., Stanford, University of California at San Francisco, Harvard, and Massachusetts Institute of Technology). Biographical data were collected on all committee members, along with their professional field, and their relationship to the given institution. (The data were obtained from membership profiles submitted to ORDA by IBCs between October 1976 and July 1978, thus some of the information may not be entirely up to date.)

In order to assess the representation of different types of members on these IBCs, individual committee members were assigned to one of nine categories. (Figure 2 on page 6 lists the nine categories.) The categories attempt to distinguish direct or indirect involvement in rDNA research and also the nature of members' affiliation with the institution. The nine categories were defined as follows: (1) Scholars in fields such as microbiology, biochemistry, or molecular genetics were categorized as scientists in rDNA disciplines. This category includes individuals most likely to be directly involved in rDNA research and represent this professional viewpoint. (2) Scholars in fields which may be related to rDNA research, such as biology, chemistry, medicine, or civil engineering, were categorized as peripherally related scientists. (3) Related administrators includes institutional and noninstitutional officials who were involved in an area related to rDNA, either research affairs or health and safety enforcement. This category includes individuals whose professional training may have been related to rDNA activitires. (4) Nonrelated scholars were those whose disciplines were totally unrelated to rDNA activities. (5) Administrators whose professional activities were unrelated to rDNA research, such as city council members or university presidents, were designated as nonrelated administrators. (6) Public representatives were individuals from the local community who were not directly associated with the institution and were not involved ir

rDNA activities. (7) Workers and (8) students were institutionally affiliated and may or may not have been involved in rDNA activities. (9) Other includes any individuals not contained in one of the preceding categories.

Results

Figure 1 shows the distribution of IBCs by size. Sizes ranged from three to nineteen, with an average size of just over ten. Committee sizes also varied by type of institution; universities tended to have somewhat larger panels (about 11 members) than noneducational institutions (about 8 members). Biographical data indicated that the committees were made up overwhelmingly of men (the average number of men and women per committee panel was 8.9 and 1.3, respectively). Also, most committee members (over 90 percent) were directly affiliated in one way or another with the university or research institution.

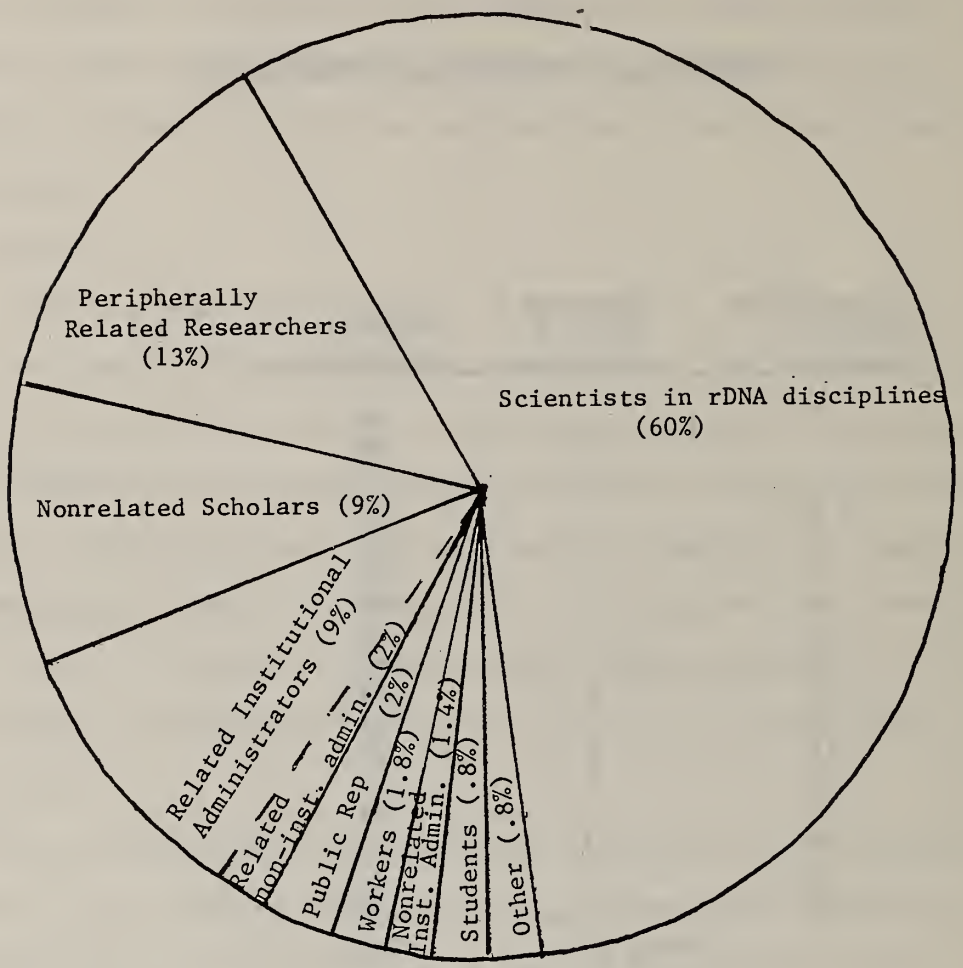
The representation of different types of members on IBCs is shown in Figure 2. The pie-shaped figure indicates the membership composition of a "typical" IBC--the average number of members per committee in each of the nine membership categories. Not surprisingly, scientists in rDNA disciplines represented the largest membership block. The representation of rDNA-related members is broader still (averaging close to 85%), if peripherally related scientists and related administrators are combined with rDNA scientists. The proportions of public members, workers, nonrelated administrators, and students each averaged less than 2 percent. Likewise, the representation of nonrelated disciplines was small--on the average, only nine percent of committee members were scholars in disciplines unrelated to rDNA. In short, the number of committee members who may be considered "nonexperts" in rDNA research was very small.

Figure 1: Distribution of IBCs by Size

Size of IBC (Number of Members)	Number of IBCs of this Size	Percent Distribution
3	1	3%
4	0	0%
5	2	7%
6	3	10%
7	5	17%
8	0	0%
9	3	10%
10	2	7%
11	3	10%
12	2	7%
13	3	10%
14	2	7%
15	0	0%
16	2	7%
17	0	0%
18	0	0%
19	2	7%
	Total 30	100%

Figure 2: Membership Composition of a "Typical" IBC

(Percent of Total Members Per Committee in Parentheses)



Categories of Members	Average Number of Members
1) Scientists in rDNA disciplines	5.8
2) Peripherally related scientists	1.3
3) Related administrators	1.2
4) Nonrelated scholars	1.1
5) Public representatives	.3
6) Workers	.2
7) Nonrelated administrators	.1
8) Students*	.1
9) Other	.1
TOTAL	10.2

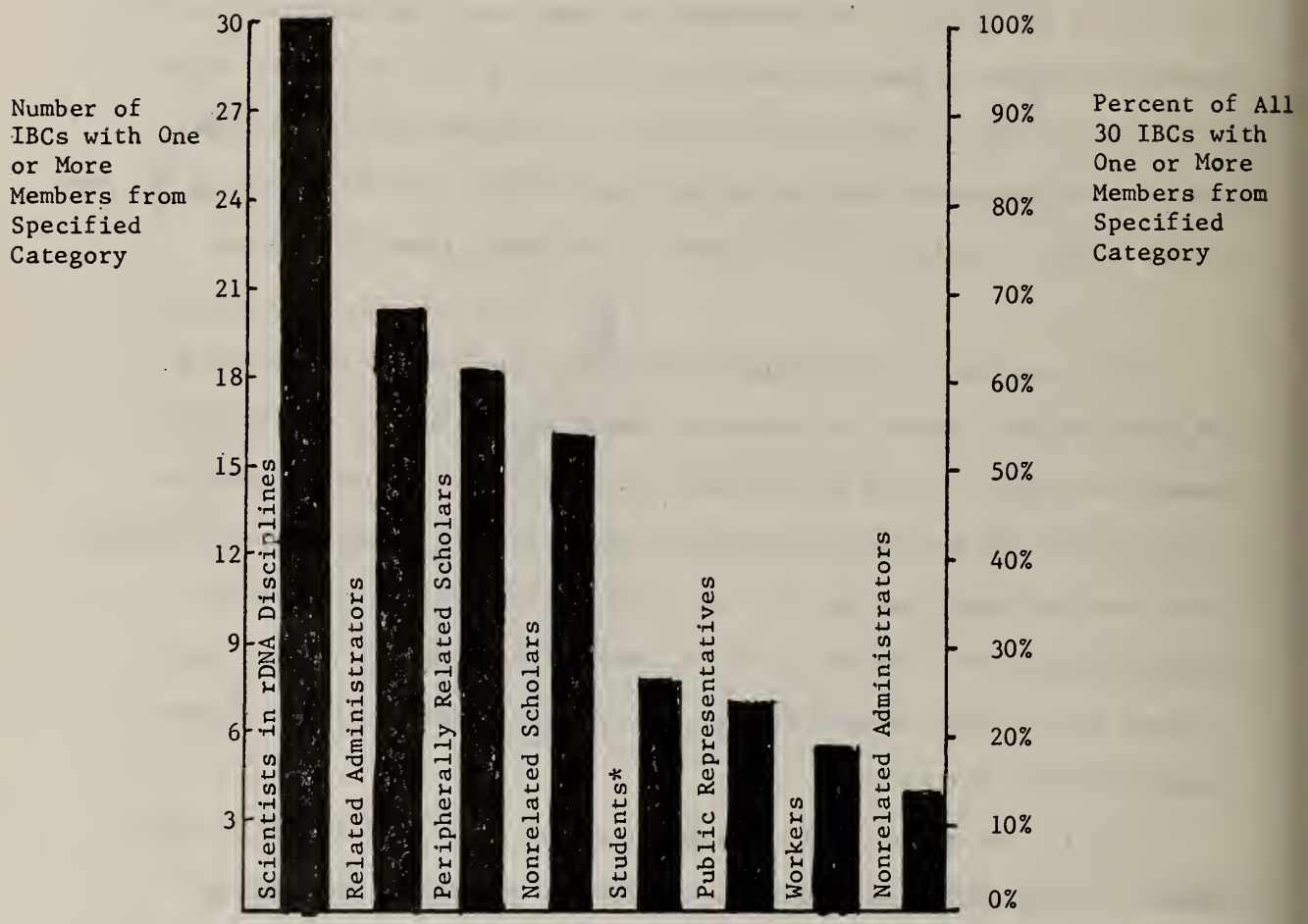
* Computed only for IBCs of educational institutions.

A similar picture emerges from an examination of each membership category in the IBCs (see Figure 3). All thirty committees had at least one scientist in an rDNA discipline, and ten percent (or three) of the committees contained only rDNA scientists. Related administrators and peripherally related scholars were each represented on about 60 percent of the IBCs in the sample. The percentage of committees with members from the nonexpert categories was much smaller; in fact,more than 70 percent of the IBCs surveyed had no representation at all of students, public citizens, workers, and nonrelated administrators, respectively. Overall, most of the IBCs in the sample included a limited number of different types of members.

With these data, one can also examine the relationship between size of committee and breadth of representation,to see whether or not larger committees result in more diversified representation. Figure 4 shows the average number of membership categories represented in committees of different sizes,and indicates that up to a size of about ten members, breadth or representation did increase with size. Beyond ten members, however (the average size of IBCs in this sample), the number of membership categories represented did not increase.

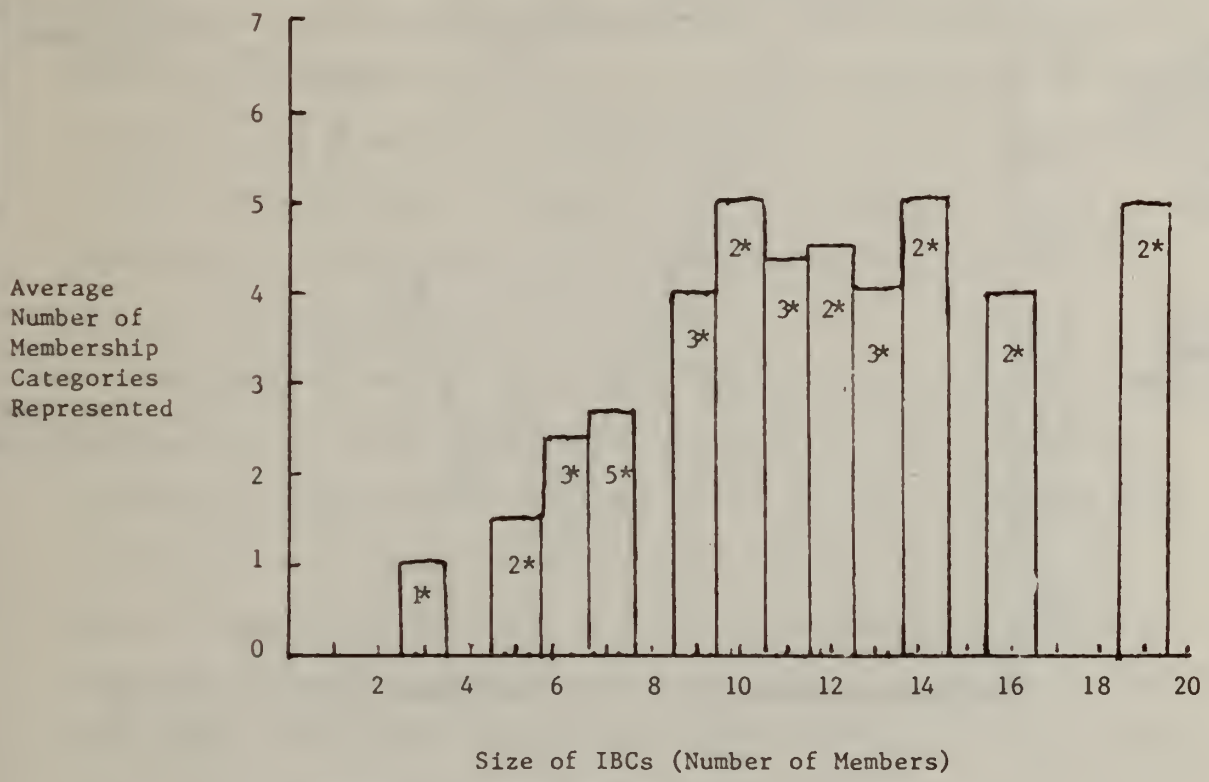
Finally, the relationship of committee size to representation of non-expert and noninstitutional members is shown in Figure 5. The average percentage of rDNA scientists on committees declines sharply with increasing committee size up to ten members, after which it levels off at about 50 percent. The representation of institutionally affiliated members, on the other hand, is essentially unrelated to committee size, averaging from 90 percent to 100 percent regardless of the number of members. Minimal representation on IBCs of noninstitutionally affiliated individuals may be an issue if it is associated with lack of responsiveness to local community concerns.

Figure 3: Number of IBCs with One or More Members from Different Categories



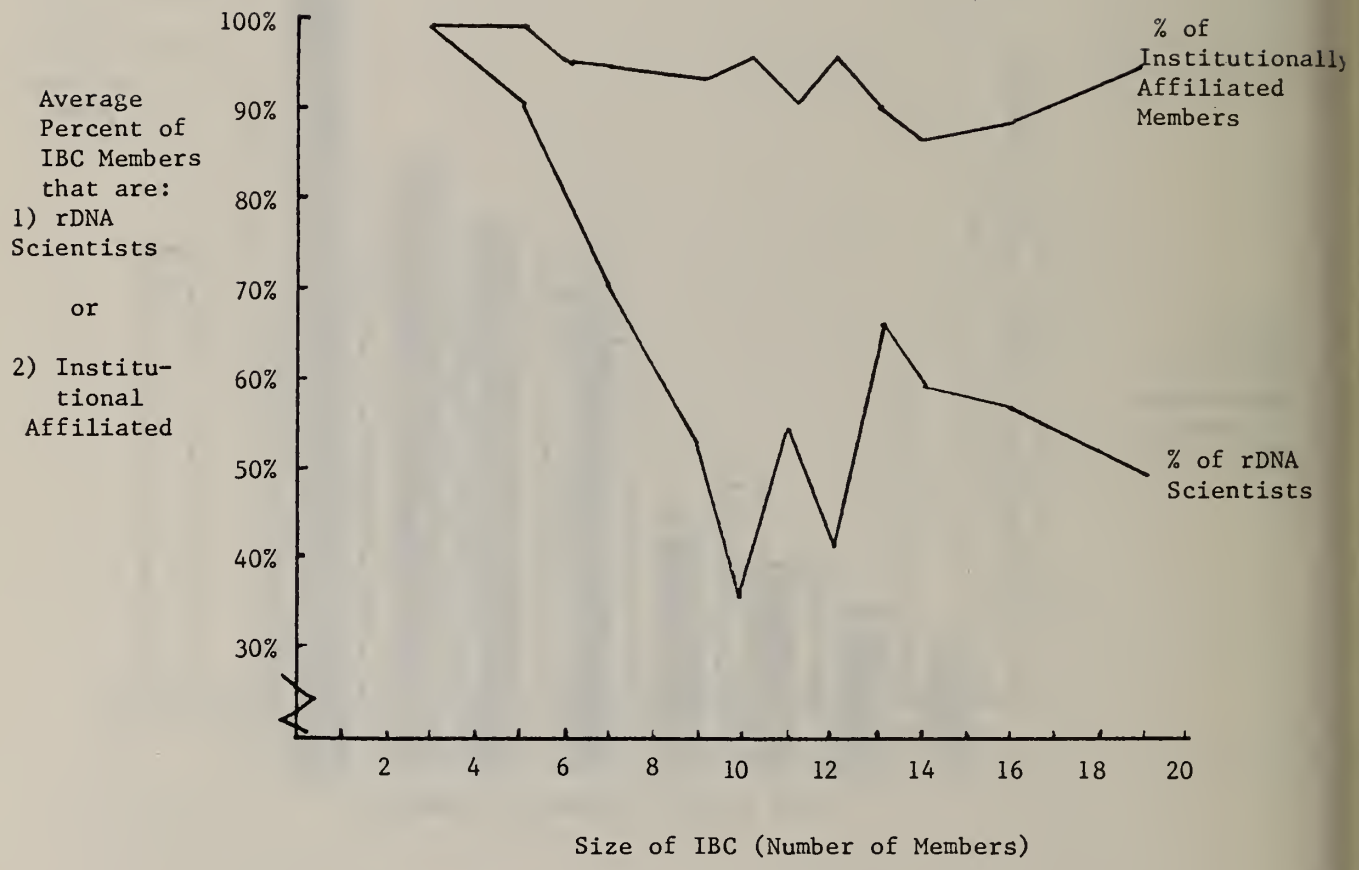
*Computed only for IBCs of the 24 educational institutions; all other category percent based on all 30 IBCs.

Figure 4: Diversity of Membership Representation by Size of IBC



* The number inside the bar indicates the actual number of IBCs with the specified number of members.

Figure 5: Composition of IBCs by Size of IBC: Percent of Scientists in rDNA Disciplines and Percent of Institutionally Affiliated Members



III. Discussion and Plans for Future Research

From the above information, it is clear that extensive public, or even nonscientific, input on IBCs remains the exception rather than the rule. The increased specificity of public and worker representation requirements in the revised guidelines may improve future opportunities for such input. However, as suggested by Figure 2, individual committees may contain so many science-oriented or 'in-house' members that even the mandatory presence of a public representative (as required in the revised guidelines) may have only a limited effect. Unfortunately, little is now known about the selection process for public and worker representatives, and it is not specified in the new guidelines; thus the degree to which these members represent a constituency or merely reflect administrative decisions already made at the institutional level, remains uncertain.

To provide information on these and issues concerning IBC structure and function, the project at Stanford with which I am working plans to undertake a two-stage research process. First, a survey will be conducted of all 150 IBCs to obtain information on the selection process for IBC members, the process and content of committee deliberations, the level of public participation in committee activities, and the degree to which IBCs are concerned with safety training and health monitoring. A sample questionnaire is enclosed. The second phase of this research will then obtain more detailed and qualitative information on committee functions and individual members' attitudes toward committee organization and actions, utilizing selective interviewing and case studies of individual IBCs. It is our hope that results will contribute to a rDNA research policy that takes into account the many aspects of committee structure and fuction which influence the

operation of IBCs and their openness to various views. With such information, future rDNA regulatory policies, specifically those which expand IBC responsibilities, could draw on facts, not assumptions, about the effectiveness and efficiency of this method of regulation.

Appendix A

Institutions Surveyed

1. University of Alabama, Birmingham
2. University of Alabama, Birmingham*
3. University of Arizona
4. University of California, Berkeley
5. Scripps Clinic and Research Foundation, La Jolla
6. University of California, San Francisco
7. Stanford University
8. National Jewish Hospital and Research Center, Denver
9. Yale University
10. George Washington University
11. Papanicolao Cancer Research Institute, Miama
12. Emory University
13. University of Hawaii, Manoa
14. University of Chicago
15. Indiana University, Bloomington
16. Johns Hopkins University
17. Childrens Hospital Medical Center, Boston
18. Harvard University
19. Massachusetts Institute of Technology
20. University of Michigan, Ann Arbor
21. Washington University, St. Louis
22. Princeton University
23. Rosewell Park Memorial Institute, Buffalo
24. Cold Spring Harbor Lab, New York
25. Cornell University
26. Columbia University
27. Memorial Sloan-Kettering Cancer Center
28. Rockefeller University
29. University of Pennsylvania
30. University of Wisconsin, Madison

* Because the University of Alabama completely reconstituted its IBC during the period in which the membership profiles were collected, both of the panels were included in the sample for this analysis and treated separately.

9/10/78

Dear Chairperson:

We are a research group at Stanford University School of Medicine which is currently studying policy issues surrounding recombinant DNA research in the United States. This study is funded by the National Science Foundation's Program in Ethics and Values in Science and Technology. In particular, we are interested in the structure and operation of Institutional Biosafety Committees (IBCs) as implied in the NIH guidelines. You have been identified, through the Office of Recombinant DNA Activities (ORDA) of the NIH as a chairperson of the IBC at your institution. We hope that you will take the time to fill out this questionnaire. This information has never been systematically assembled, and is of great potential significance to all those concerned with efficiency and equity in recombinant DNA regulation.

In addition, we would like to receive copies of the following documents, if available:

a) a list of members' names and titles or positions
b) the administrative charge, bylaws, and/or operating rules of your panel
c) official documents pertinent to educational and/or policy issues of your committee.

We appreciate your participation in this survey, and look forward to hearing your comments and questions. In turn, we will arrange for a tabulation of the survey results to be made available to all IBCs. For forther information feel free to contact us at:

Health Services Research, Stanford University
703 Welch Road, Suite G-1
Stanford, California 94305 (415) 497-6426.

Sincerely, Diana B. Dutton, Ph.D., Principal Investigator
John P. Bunker, M.D., Co-principal Investigator
Health Services Research, Stanford University School of Medicine

STRUCTURE OF COMMITTEES

1. Please list the number of members of your panel that are:	Total Number	Of these totals, how many are: Involved in rDNA-related issues outside the IBC	Women	Minorities
scientists or MDs engaged in rDNA research				
biologists, chemists, or MDs not engaged in rDNA research				
other natural or physical scientists or engineers (not included in above)				
other faculty/scholars in the humanities, social sciences and professions				
institutional health and safety officers				
other institutional administrators				
students				
workers/technicians				
local government representatives (e.g., health dept.)				
public citizens				
Other (please describe) _____				
TOTAL number of panel members:				

2. How are committee members chosen? (please check all that apply:
   - ☐ administrative appointment
   - ☐ nominations or election by faculty
   - ☐ nominations or election by students
   - ☐ nominations or election by workers
   - ☐ nominations or election by local governments
   - ☐ ex officio membership
   - ☐ other (please describe) _____

3. Do all members of the committee have an equal vote in processing MUAs and other committee business: (MUAs=Memoranda of Understanding and Agreement)
   ☐ Yes ☐ No (please explain:) _____

4. How many months is the term of appointment for your committee members?
   ____ number of months
   a. If different lengths for different members, please describe: _____

5. Are any members eligible to serve more than one consecutive term?
   ☐ No (skip to Question 6)

   If yes, which ones? _____

6. What relationship does the committee have to

	serves in advisory capacity	has independent decision-making authority
Institutional Administration		
Local Government		
Other (please describe):		

7. What financial resources are available to the committee? (please check all that apply) (For each source, please estimate the rough $amount during the past 12 months.)

   - ☐ Earmarked institutional funds $ _____
   - ☐ Discretionary department funds of committee members $ _____
   - ☐ Health and safety office funds $ _____
   - ☐ Other (please describe): _____ $ _____

PROCESS OF THE COMMITTEES

8. How many of the members must be present to hold a meeting?
___Number of members ☐No such requirement (skip to question 7)

a. If there are any special requirements by type of member, please describe: _____

_____

b. About how many meetings in the past year have been cancelled due to lack of a quorum?
___Number of meetings

9. How often have full committee meetings been held during the last year?
☐weekly ☐every two weeks ☐monthly ☐quarterly ☐on an irregular basis ☐other (please specify):

_____

10. Is there a standard meeting time? ☐No ☐Yes: If yes, what time of day?
☐morning ☐lunchtime ☐afternoon ☐evening

11. On the average, how long do the meetings last?
☐less than one hour ☐one to two hours ☐more than two hours

12. What is the rough percentage of committee time spent discussing research proposals (MUAs) versus policy questions or general procedural issues?
___% time spent on research proposals
___% time spent on policy or procedural issues
___% time spent on other committee business (please describe): _____

_____

_____

a. Please list some of the major policy questions and procedural issues discussed in the last year:

Policy	Procedure
_____	_____
_____	_____
_____	_____
_____	_____

13. Which of the following mechanisms are used to inform non-rDNA scientists on the committee about the technical content of MUAs (please check all that apply):
☐rDNA scientists prepare written summaries of MUAs in less technical language
☐educational presentations on scientific and technical matters
☐rDNA scientists present verbal summaries of MUAs
☐other (please describe) _____

_____

14. Please estimate the rough percentage distribution of the funding sources of rDNA research under your jurisdiction:
___% federal government ___% private foundation ___% private industry
___% other (please describe) _____

15. Does your committee process MUAs for any organization not formally related to your institution?
☐No ☐Yes: (please describe) _____

_____

PUBLIC PARTICIPATION

16. How many meetings are open to the public? ☐All ☐Some ☐None (skip to Question 17)

a. Can representatives of the public: (please check all that apply)
☐ask questions throughout the meeting?
☐ask questions during certain parts of the meeting?
☐make statements or presentations throughout the meeting?
☐make statements or presentations during certain parts of the meeting?

b. Is the agenda restricted in any way during open meetings?
☐No ☐Yes If yes, how? _____

_____

17. Which of the following mechanisms are used to inform the public about committee proceedings? (please check all that apply)
☐meetings are publicized (e.g., community notices or newspaper advertisements)
☐agendas are mailed to interested people prior to meetings
☐minutes are mailed (or circulated) to interested people following meetings
☐educational forums for the public have been sponsored
☐other (please describe) _____

_____

HEALTH AND SAFETY TRAINING AND MONITORING

18. Is there a single individual, such as a biological safety officer, responsible for matters of health, training, and enforcement regarding rDNA research?

☐No ☐Yes If yes, individual's title: _____

a. About what percentage of this individual's time is spent on rDNA activities? _____%

19. Which of the following measures are taken to ensure institutional compliance with committee regulation decisions? (please check all that apply)
☐procedural conditions attached to approved MUAs
☐responsibility delegated to institutional health and safety officer
☐unannounced visits to laboratories
☐consultation with principal investigators or other rDNA personnel
☐inspection of lab log books
☐other (please describe) _____

_____

20. Does your institution have health monitoring programs for those involved in rDNA research?

☐No ☐Yes If yes, please describe: _____

_____

21. Does your institution have worker training programs for those employed in or around rDNA laboratories?

☐No ☐Yes If yes, please describe: _____

_____

ANY OTHER COMMENTS? _____

_____

_____

STATEMENT BY FRANK H. RUDDLE

Department of Biology, Yale University

My name is Frank H. Ruddle. I speak for no organized group, but mainly for myself. I am a cell biologist and geneticist. I have been a faculty member in the Department of Biology, Yale University since 1961, in which I now serve as chairman. At Yale I served as chairman of the Biological Safety Advisory Committee, which regulates recombinant DNA research at our university. I am proud of the fact that the city of New Haven is actively represented on that committee. All meetings are open to the public. There is to my knowledge no opposition within the university or the city to implementation of the revised guidelines.

My professional interest is somatic cell genetics. This discipline is concerned with an understanding of the genetic organization and function of mammalian chromosomes, especially those of man. An important technique in my studies is cell hybridization, which permits one to literally fuse mouse and human cells to produce viable, healthy hybrid cells which can be propagated in tissue culture. In such hybrid cell populations, one can trace the loss of human chromosomes and correlate that loss with particular human traits. In this way it has been possible to use hybrid cells to map human genes to particular human chromosomes. Since 1970 more than 200 genes have been mapped in man using this technique.

The basic knowledge gained has contributed to our understanding of primate evolution and the mode of action of gene mutations which result in specific genetic abnormalities. Citing a specific case, these studies have resulted in a better understanding of the genetic control of the interferon system, which is instrumental in protecting the organism from viral infection and which shows promise as an anticancer therapeutic agent. Also, information has been provided on many other interesting and important biological systems.

Until the advent of the recombinant DNA technology, the somatic cell genetic technique could only analyze the human genetic material at a low level of resolution. Making use of recombinant DNA procedures, it is now possible to continue the study of human genetics at very high levels of resolution.

Using nucleic hybridization techniques, our laboratory in collaboration with an NIH research group has recently mapped the human genes for the α and β globins. This knowledge now provides new possibilities for experiments dealing with a better understanding of the control of hemoglobin expression with obvious relevance to genetic, developmental, and environmentally induced abnormalities involving human hemoblobins.

We are now beginning to use cloned globin DNA sequences for this purpose--a method which is far simpler, faster, more reliable, and cheaper than those previously employed.

It should also be strongly emphasized that many biologically important human genes will be mapped in man only by using recombinant DNA technology in concert with the somatic cell genetic procedure. There is no question in my mind that our understanding of human genetics and its development depends importantly on the use of recombinant DNA methodologies. It also follows that the reduction of containment of human and mammalian DNA to PK2/EK2 from P3/ or P4/EK2 will make a huge difference in our rate of progress in human genetics.

There is another scientific development which is pertinent to our deliberations here today. Recent experiments performed at Columbia University have shown that it is possible to transform mammalian cells--that is to say, to introduce functional genes into cells--by simple exposure to mammalian DNA. This will provide a means of purifying particular kinds of human genes using DNA-mediated transformation as a bioassay. Alternative techniques for achieving the same purpose make use of deleted animal viruses such as SV40. It is clear to all that the availability of cloned mammalian genes will provide a very great impetus to our knowledge of the human gene map and the control of expression of human genes. Also, the isolation of human genes by cloning represents the first step in the pharmaceutical production of therapeutic proteins such as insulin, blood clotting factors, interferons, and a host of additional medically important products.

The rapidity with which such products become available to the public will be significantly influenced by the stringency of the recombinant DNA guidelines. It seems ludicrous that some of our most productive and creative scientists have felt it necessary to carry out their investigations in Europe because of the unrealistically stringent regulations now in effect. This practice if continued will only serve to weaken United States biomedical science. Certainly, the reduction of containment levels for eukaryotic cells and for animal viruses is very much in order.

There is one additional point I would like to make. In connection with the transformation experiments which I mentioned previously, we have been isolating in our laboratory a small segment of the Herpes simplex virus chromosome containing a particular gene. We are forced to do this by growing up large quantities of the live virus. This practice is expensive, time-consuming, and cumbersome. We would prefer not to deal with large amounts of live virus because of the risk of possible exposure of laboratory personnel. It would of course be possible to clone the Herpes chromosome fragment of interest using existing recombinant DNA techniques. Such a practice would be far simplier, faster, and cheaper than growing the intact virus. From a biosafety viewpoint, I would judge the recombinant DNA cloning of the Herpes fragment to be in itself innocuous and certainly far safer than growing the virus. This kind of cloning

experiment is not currently possible at P3 levels of containment under the provisions of the existing guidelines. It could be readily done under the revised guidelines.

In closing, let me say a few words about biological risk. Our Department of Biology at Yale covers a broad spectrum of the biosciences ranging from molecular biology to the environmental sciences. None of my faculty members have expressed concern over these pending revisions in the recombinant DNA guidelines. Throughout the whole university, including the school of medicine, there is, in fact, broad and strong support for the implementation of the revised guidelines. I believe we should not lose sight of the fact that the risk associated with recombinant DNA organisms has not been established, much less measured or quantitated. On the other hand, the risks of disease, aging, birth defects are well established and altogether too real.

The recombinant DNA technology can contribute in a major way to our understanding of basic biological phenomena; and this knowledge, in turn, is bound to provide practical ways of dealing with the very real medical problems of mankind. I believe that the implementation of these new, revised guidelines is in the best interest of the public--and that they should be approved at the very earliest time. I personally endorse them wholeheartedly.

September 15, 1978

COMMENTS ON THE PROPOSED REVISED GUIDELINES FOR RECOMBINANT DNA RESEARCH BY:

Oscar L. Miller, Jr., Ph.D., Professor and Chairman, Department of Biology of the University of Virginia and Member of the National Academy of Sciences.

As a non-user, I would like to briefly comment on the Proposed Revised Guidelines from three points of view: in my capacity as Chairman of a department in which recombinant DNA research is ongoing, in my capacity as head of an institutional committee charged with evaluation of the need and feasibility for a P3-level Physical Containment Facility, and as a colleague and friend of many of the scientists involved in the use of recombinant DNA techniques to study the structure and regulation of genetic activity.

As chairman of a department containing faculty members interested in using recombinant DNA techniques, I have an obligation to foster conditions that will advance the careers of such faculty; but I also have a higher obligation to insure the safety of all the personnel of my department from biohazards of all kinds. As it became evident that recombinant DNA techniques would be powerful experimental probes, we early-on held open departmental meetings to discuss the pros and cons of the use of such techniques. After careful consideration of the original Guidelines and conversations with trusted knowledgeable colleagues in this field, I became convinced that the recombinant experiments being proposed by certain members of my faculty would be safe if carried out under the conditions required by the Guidelines. To this end, I supported the appointment of an institutional Committee on Recombinant DNA Research responsible for the approval and monitoring of physical containment facilities and the experiments done therein. The committee as appointed contains, in addition to knowledgeable basic biological scientists,

representatives from the areas of city and county governments, science law, and epidemiological medicine. Similar knowledgeable and broad-based representation is characteristic of analogous committees at other universities with which I am familiar, indicating that institutions and their scientists are acting in a highly responsive way to the need to safeguard communities while at the same time allowing valuable recombinant DNA research to continue. The responsible records of local committees in implementing the current Guidelines argues well for their abilities to assume increased authority under the Revised Guidelines in a manner that will continue to assure safety from potential biohazards for those living in their communities.

Since members of my department were interested in carrying out research using recombinant DNA techniques, I was asked by my institution to form a special committee to evaluate the need and feasibility for a P3-level Physical Containment Facility. The need and feasibility for a facility was soon established and a successful proposal for matching funds was made to NIH. A three-member users committee was proposed to oversee the actual day-to-day operation of the facility, with this committee to be closely monitored by the institutional committee. Again, my interactions with the institutional committee in my endeavor to obtain a P3 facility reinforced my strong belief that such committees will continue to responsibly carry out their assigned duties under the Revised Guidelines.

I have the pleasure of knowing many of the scientists who are carrying on highly significant research projects using recombinant DNA techniques, some of whom have been involved in the formation of the original Guidelines and the current proposed Revised Guidelines. I count several of these investigators as good friends. As a group, they are highly motivated, highly intelligent, and intellectually honest scientists who are respected in their communities.

I find, perhaps unexpectedly, that they are also quite gentle people. In addition, those whom I have been priviledged to know in family situations have always demonstrated a deep affection for their spouse and children. Knowing these people as I do, it is inconceivable to me that any of them would put rapid career advancements made possible by unsafe biohazardous techniques ahead of their concern for the safety of their families and communities. I have the highest respect for the intellectual and moral honesty of these scientists, and their considered study and approval of the Revised Guidelines is, in my opinion, the strongest recommendation for their adoption.

September 15, 1978

A STATEMENT IN SUPPORT OF THE ADOPTION OF THE PROPOSED REVISED GUIDELINES FOR RECOMBINANT DNA RESEARCH PREPARED BY CHARLES P. EMERSON, JR, PHD. AND MICHAEL KUEHL, MD, OF THE UNIVERSITY OF VIRGINIA.

I am Charles Emerson, Associate Professor of Biology at the University of Virginia. I would like to read a statement in support of adoption of the revised Guidelines for Recombinant DNA Research. This statement was prepared by myself and Dr. Michael Kuehl of the Department of Microbiology, and reflects our views as well as those of Drs. Robert Grainger and Robert Devlin of the Department of Biology and Drs. Thomas Parsons, Carolyn Collins and William Steinberg of the Department of Microbiology at the University of Virginia.

We are molecular biologists whose research programs are focused on understanding the mechanisms of gene regulation in higher organisms. Specifically, we are studying a variety of problems which include, for example, the molecular basis of gene regulation during embryonic development of avian and human muscle, genetic control of antibody formation, and expression of tumor viruses in avian and mammalian cells. Our research programs have been and will continue to be profoundly influenced by the information and the ideas resulting from recombinant DNA reasearch and will be greatly affected by any Guidelines imposed on this area of research.

We agree that the current Guidelines (June 23, 1976), which have imposed stringent restrictions on experiments involving recombinant DNA technology during the past few years, were appropriate. This period

of extreme caution has served the useful function of permitting a thourough evaluation of potential risks of such experiments. However, despite efforts by scientists, environmentalists, lay people, etc., to conjure up worst case scenarios of potential hazards, there is no evidence to support the contention that recombinant DNA research poses a biohazard to humans or their environment. Arguments that biohazardous organisms may be produced by recombinant DNA research appear to us to be simply speculation with no basis in fact and no foundation in our understanding of biological processes.

In view of the lack of evidence for creation of significant biohazards through recombinant DNA research, the lowering of physical containment requirements in the proposed revised Guidelines is entirely appropriate. In addition, the revised Guidelines can be expected to have considerable positive impact on recombinant DNA research in this country. This is an issue to which we can speak to from our own research experience. The current Guidelines have imposed stringent physical containment requirements, P3 or P4, for studies involving higher organisms. The requirement for these extreme levels of physical containment have made it difficult and in many cases impossible to use this important technique for studies involving genetic material from higher organisms. P3 facilities are costly to construct and to maintain. And many institutions such as our own have not had the resources to establish such facilities. In my own case I have undertaken some recombinant DNA experiments at a P3 facility located at another institution a considerable distance from Virginia. As a result of the enormous complications and inconvenience of this arrangement, my research program

has been set back at least a year. Dr. Kuehl and our other colleagues have not even attempted to use recombinant DNA techniques in their research because of the lack of a P3 facility at Virginia, in spite of the importance these techniques would have for their research programs.

The proposed revised Guidelines are a consevative step in relaxing the requirements for physical containment for recombinant DNA research. However adoption of these revised Guidelines will serve the dual purpose of continuing to greatly minimize the possible risks of recombinant DNA research, while at the same time providing conditions which will permit the realization of the huge benefits which will derive from this technique.

OARDC
Ohio Agricultural Research and Development Center
WOOSTER, OHIO 44691
TELEPHONE (216) 264-1021

DEPARTMENT OF
PLANT PATHOLOGY

September 14, 1978

TO: HEW Review Committee on Recombinant DNA Guidelines

FROM David L. Coplin
Assistant Professor of Plant Pathology
Ohio Agricultural Research and
Development Center
The Ohio State University

SUBJECT: Summary of comments on proposed revised guidelines for recombinant DNA research given at the public hearing on September 15, 1978.

As a plant pathologist, I am greatly concerned that the stringent regulations placed on research with plants and plant associated microorganisms by the current guidelines for recombinant DNA have greatly delayed the use of this technique in such areas as genetic improvement of plants, biological nitrogen fixation and the study of plant diseases. Addressing my own area of expertise, the cost of plant diseases is tremendously high in terms of crop losses and the expense of control measures. Since pesticide usuage is decreasing, there is a need , now more than ever, for basic research on plant pathogens so that new methods of controlling them can be devised. At present it is not known exactly what properties enable only certain specialized pathogens to cause plant disease. Physiologists have been handicapped in their approaches to this problem due to the lack of good genetic systems to use in identifying virulence genes and constructing strains for biochemical studies. Recombinant DNA techniques now offer an opportunity to study the genetics of plant pathogenic bacteria for which usable gene transfer systems have not been developed and to purify genes for virulence, work with them in a known genetic background, determine their genetic organization and characterize their gene products. This approach is much faster, less equivical, and has a better chance for success than by doing the same experiments using classical genetic techniques.

The current guidelines place unnecessarily high containment levels (P2 or P3) on recombinant molecules formed from DNA from plants, plant symbionts, and plant pathogens (viruses, bacteria and fungi). These restrictions arose from unfamiliarity on the part of the authors of the guidelines with these organisms and their assumptions that many possibly dangerous plant products are determined by single genes and that plant pathogens are equally as infectious and dangerous as the animal pathogens found in CDC class 2. This is simply not correct. Other problems concerning plant pathogens are the prohibition on restoring virulence

to avirulent mutants and the need to certify new host-vector systems for self cloning experiments or so that DNA cloned into E. coli can be returned to its host of origin. Another problem which concerns geneticists, regardless of whether or not they are involved with cloning, is that in vitro constructed plasmids cannot be transferred from E. coli to other bacteria even though they are merely deleted plasmids or have been formed from plasmids which have already been shown to transfer to the species in question without adverse effect. This greatly limits the genetic tools available to workers in other fields.

As a result of the current restrictions, recombinant DNA techniques have not been widely used in the plant sciences. Agricultural workers are often obligated to divide their efforts between so called basic and applied programs and are seldom full time geneticists. They are not in a position to afford new containment equipment which up to now has not been needed for their work, reallocate space currently shared with other programs for P2 or P3 facilities and devote their time to research for the sole purpose of documenting the safety of their host-vector system.

The revised guidelines eliminate many of the problems mentioned above by exempting or reducing the containment required for studies with DNA from plants and plant associated microorganisms and viruses. I fully agree with the rationale for these changes as presented in the report of The Workshop on Risk Assessment of Agricultural Pathogens. If these guidelines are implemented there will certainly be an increase in the number of plant scientists using this technique and the benefits to agriculture could be tremendous. I, for one, am not currently working with recombinant DNA but would like to use the technique, if new guidelines are implemented, to investigate the association between plasmids and virulence in Erwinia stewartii, a pathogen of corn.

On behalf of other plant pathologists I strongly urge that the proposed Revised Guidelines be accepted and implemented as soon as possible so that there will be no further delays in beginning important research on genetic improvement of plants, nitrogen fixation and plant diseases.

TESTIMONY FOR HEW PUBLIC HEARINGS ON PROPOSED REVISED GUIDELINES

FOR RECOMBINANT DNA RESEARCH

September 15, 1978

David L. Coplin, Assistant Professor, Ohio Agricultural Research and Development Center, The Ohio State University, Wooster, Ohio 44619

I AM A ASSISTANT PROFESSOR OF PLANT PATHOLOGY AT THE OARDC WHICH IS THE AGRICULTURAL EXPERIMENT STATION FOR THE OHIO STATE UNIVERSITY AND A MEMBER OF THE AMERICAN PHYTOPATHOLOGICAL SOCIETY SPECIAL COMMITTEE ON RECOMBINANT DNA. MY TRAINING IS IN BOTH PLANT PATHOLOGY AND BACTERIOLOGY AND I AM CURRENTLY STUDYING THE GENETICS OF PLANT PATHOGENIC BACTERIA.

AS PLANT SCIENTIST, I AM CONCERNED THAT GENETIC STUDIES ON PLANTS AND PLANT PARASITES HAVE BEEN DELAYED UNDER THE PRESENT GUIDELINES FOR RECOMBINANT DNA RESEARCH. TODAY I WILL BE ADDRESSING THE PROPOSED REVISED GUIDELINES FROM THE VIEWPOINT OF A PLANT PATHOLOGIST. EACH YEAR THE COST OF PLANT DISEASES TO THIS COUNTRY IS VERY HIGH IN TERMS OF CROP LOSSES AND THE EXPENSE OF CONTROLLING THEM. DUE TO CONCERNS FOR OUR ENVIRONMENT AND THE PUBLIC SAFETY MANY PESTICIDES HAVE BEEN TAKEN OFF THE MARKET AND RELATIVELY FEW NEW ONES ARE BEING DEVELOPED. THIS SITUATION INCREASES OUR NEED FOR BASIC RESEARCH IN PLANT PATHOLOGY SO THAT NEW CONTROL PROCEDURES CAN BE DEVISED. AT PRESENT, IT IS NOT KNOWN EXACTLY WHAT PROPERTIES ENABLE ONLY CERTAIN SPECIALIZED PATHOGENS TO CAUSE DISEASE WHILE CLOSELY RELATED SPECIES CANNOT. LIKEWISE, WE DO NOT KNOW EXACTLY HOW PLANTS RECOGNIZE POTENTIAL PARASITES. DISEASE PHYSIOLOGISTS STUDYING PLANT PATHOGENS AND DISEASE RESISTANCE HAVE BEEN HANDICAPPED IN THEIR APPROACHES TO THESE PROBLEMS DUE

TO THE LACK OF GOOD GENETIC SYSTEMS FOR THEIR USE IN IDENTIFYING GENES FOR VIRULENCE AND CONSTRUCTING STRAINS TO USE IN BIOCHEMICAL STUDIES.

PLANT PATHOGENIC BACTERIA MAKE EXCELLENT MODEL SYSTEMS FOR BASIC STUDIES ON HOST-PARASITE RELATIONSHIPS BECAUSE THE GENETICS OF THE HOST AND PARASITE CAN BE STUDIED IN PARALLEL. THE FINDING THAT MEMBERS OF THE GENERA PSEUDOMONAS, ERWINIA, AND AGROBACTERIUM NATURALLY EXCHANGE DNA WITH E. COLI AND P. AERUGINOSA HAS GIVEN US THE KEY TO DOING MOLECULAR GENETICS WITH THEM. AS A RESULT, THIS IS ONE OF THE MOST ACTIVE AND PROMISING FIELDS OF PLANT PATHOLOGY TODAY. BUT EVEN SO THERE ARE ONLY ABOUT A DOZEN LABORATORIES INVOLVED IN THIS RESEARCH IN THE UNITED STATES TODAY AND THEIR EFFORTS ARE DIVIDED AMONG A NUMBER OF PATHOGENS. BECAUSE MANPOWER IS LIMITED AND BECAUSE WE ARE WORKING WITH GENETICALLY UNCHARACTERIZED BACTERIA, IT IS IMPERATIVE THAT WE TAKE ADVANTAGE OF THE BEST TECHNOLOGY AVAILABLE TODAY. ALTHOUGH SUCH STUDIES COULD POSSIBLY BE DONE BY CLASSICAL GENETICS, THE RECOMBINANT DNA TECHNIQUE OFFERS US A USEABLE MEANS OF GENETIC EXCHANGE FOR ORGANISMS IN WHICH GENE TRANSFER IS NOT CHARACTERIZED AND IT OFFERS ONE THE ADDED ADVANTAGE OF BEING ABLE TO PURIFY GENES FOR VIRULENCE OR HOST SPECIFICITY, STUDY THEIR GENETIC ORGANIZATION, AND CHARACTERIZE THEIR GENE PRODUCTS. THE RECOMBINANT DNA APPROACH IS FASTER, LESS EQUIVOCAL AND HAS A GREATER CHANCE FOR SUCCESS THAN IF THE SAME EXPERIMENTS WERE DONE USING CONJUGATION OR TRANSDUCTION. SIMILAR EXPERIMENTS HAVE ALREADY PROVEN VALUEABLE IN THE STUDY OF ANIMAL DISEASES. I MIGHT ADD HERE THAT THE PROBLEM OF NODULATION BY NITROGEN FIXING BACTERIA IS VERY SIMILAR TO THE PROBLEM OF HOST SPECIFICITY IN PLANT PATHOGENS, AND THAT THE SAME RATIONALE APPLIES TO THE FIELD OF NITROGEN FIXATION. IN ADDITION STUDIES ON THE GENOMES OF PLANT VIRUSES AND AGROBACTERIUM TUMEFACIENS MAY

RESULT IN THE DISCOVERY OF A MECHANISM FOR INSERTING NEW GENES INTO PLANTS.

THE CURRENT GUIDELINES ESTABLISHED IN 1976 HAVE UNNECESSARILY RESTRICTED THE CLONING OF DNA FROM PLANTS AND FROM PLANT PATHOGENIC FUNGI, BACTERIA, AND VIRUSES IN SEVERAL WAYS: i) MOST PERMISSIBLE EXPERIMENTS WITH DNA FROM THESE SOURCES REQUIRE P2 OR P3 CONTAINMENT. THIS RESTRICTION APPEARS TO HAVE BEEN BASED ON THE UNFAMILIARITY OF NIH WITH PLANTS AND THEIR PARASITES RATHER THAN ON EVIDENCE OF GREATER RISK INVOLVING THESE ORGANISMS, ii) THERE IS A PROHIBITION ON EXPERIMENTS WHICH MIGHT INCREASE THE VIRULENCE AND HOST RANGE OF A PLANT PATHOGEN, AND THIS IN EFFECT RULES OUT COMPLEMENTATION STUDIES WITH AVIRULENT MUTANTS AND iii) THERE IS A REQUIREMENT THAT ALL HOST VECTOR SYSTEMS BE CERTIFIED BEFORE ONE CAN DO SELF CLONING EXPERIMENTS OR REINTRODUCE DNA, WHICH HAS BEEN CLONED INTO E. COLI BACK INTO ITS HOST OF ORIGIN. THE LATTER EXPERIMENT IS, OF COURSE, NECESSARY IF GENES FOR PATHOGENICITY OR NODULATION ARE TO BE STUDIED SINCE THESE PROPERTIES WOULD NOT BE EXPRESSED IN E. COLI. MOREOVER, THIS REQUIREMENT FOR CERTIFICATION OF HOSTS CREATES PROBLEMS EVEN FOR THE GENETICIST NOT INVOLVED IN RECOMBINANT DNA RESEARCH. MANY VERY USEFUL PLASMIDS HAVE BEEN CONSTRUCTED IN E. COLI BY RESTRUCTURING DRUG RESISTANCE PLASMIDS IN VITRO. AT PRESENT, THESE PLASMIDS CANNOT BE TRANSFERRED TO OTHER BACTERIA WITHOUT PRIOR NIH APPROVAL EVEN THOUGH THE PARENT PLASMIDS HAVE BEEN INTRODUCED INTO THE SPECIES IN QUESTION WITHOUT APPARENT DANGER.

THESE REQUIREMENTS FOR HIGH CONTAINMENT LEVELS AND CERTIFICATION OF HOST VECTOR SYSTEMS HAVE DISCOURAGED THE USE OF CLONING IN WORK WITH PLANTS, NITROGEN FIXERS AND PLANT PATHOGENS. AGRICULTURAL SCIENTISTS ARE OFTEN

OBLIGATED TO DIVIDE THEIR TIME BETWEEN SO CALLED BASIC AND APPLIED PROGRAMS AND ARE SELDOM FULL TIME GENETICISTS. THEY SIMPLY DO NOT HAVE THE TIME TO DO THE EXTRA PAPERWORK AND RESEARCH NEEDED TO CERTIFY THEIR SYSTEMS. FURTHERMORE CONTAINMENT AND SAFETY EQUIPMENT HAS RARELY BEEN NEEDED IN THE PLANT SCIENCES SO THAT COMPLIANCE WITH THE GUIDELINES WOULD REQUIRE NEW PURCHASES WHICH YOUNG INVESTIGATORS MAY NOT BE ABLE TO AFFORD. IN ADDITION, ESTABLISHMENT OF P2 AND P3 FACILITIES WOULD INFRINGE ON LAB SPACE ORIGINALLY SHARED WITH OTHER PROJECTS.

THE PROPOSED REVISIONS TO THE GUIDELINES SOLVE MANY OF THESE PROBLEMS BY i) EXEMPTING OR LOWERING THE CONTAINMENT LEVELS REQUIRED FOR EXPERIMENTS WITH SOME OF THE BETTER CHARACTERIZED SYSTEMS, ii) EXEMPTING SELF CLONING EXPERIMENTS AND iii) MAKING PROVISION FOR TRANSFER OF CLONED DNA BACK TO ITS HOST OF ORIGIN AT A P1 LEVEL. THE ONLY POSSIBLE DIFFICULTY WITH THE REVISED GUIDELINES THAT HAS COME TO MY ATTENTION IS A GENERAL CONCERN ON THE PART OF SCIENTISTS ON JUST HOW MUCH DOCUMENTATION AND THE TIME THAT MIGHT BE REQUIRED TO CHANGE THE CLASSIFICATION OF A PARTICULAR EXPERIMENT OR ADD NEW ORGANISMS TO THE LIST OF GENE EXCHANGERS. HOWEVER, IT IS COMMENDABLE THAT A MECHANISM FOR SUCH CHANGE HAS BEEN PROVIDED.

IN REFERENCE TO THE EVIDENCE ON WHICH THESE REVISIONS ARE BASED, I AM IN FULL AGREEMENT WITH THE RATIONALE SET FORTH BY THE WORKSHOP ON RISK ASSESSMENT OF AGRICULTURAL PATHOGENS AND I FEEL THAT THEIR CONCLUSIONS ARE BASED ON SOUND PRINCIPLES OF PLANT PATHOLOGY. SPECIFICALLY THEY CONCLUDED THAT INTRODUCTION OF DNA FROM PLANT PATHOGENS INTO E. COLI K12 WILL NOT MAKE IT HARMFUL TO MAN, ANIMALS OR PLANTS. MOREOVER IT SHOULD BE NOTED THAT RESISTANCE TO MICROORGANISMS AMONG PLANTS IS MORE COMMON THAN SUSEPTIBILITY AND THAT FOR AN

EPIDEMIC TO OCCUR YOU MUST SIMULTANEOUSLY HAVE LARGE NUMBERS OF SUSEPTIBLE PLANTS IN ONE LOCATION, JUST THE RIGHT WEATHER CONDITIONS AND HIGH POPULATIONS OF THE PATHOGEN. AS A RESULT PLANT PATHOGENS GENERALLY HAVE RESTRICTED HOST RANGES AND GEOGRAPHIC DISTRIBUTION. CONSEQUENTLY, I BELIEVE THAT IT SHOULD BE JUST AS SAFE TO WORK WITH THE RECOMBINANT DNA MADE FROM PLANT PATHOGENS AS IT IS TO WORK WITH THE PATHOGENS THEMSELVES.

I HAVE SPOKEN WITH A NUMBER OF PLANT PATHOLOGISTS CONCERNING THE PROPOSED REVISIONS AND ALL OF THEM ARE ANXIOUS TO SEE THE NEW GUIDELINES IMPLEMENTED AS SOON AS POSSIBLE. WHEN THE PROPOSED REVISED GUIDELINES ARE ACCEPTED THERE WILL CERTAINLY BE AN INCREASE IN THE NUMBER OF PLANT SCIENTISTS USING THIS TECHNIQUE AND THE BENEFITS TO AGRICULTURE COULD BE TREMENDOUS. I, FOR ONE, WOULD LIKE TO USE CLONING TO ESTABLISH THE RELATIONSHIP BETWEEN PLASMIDS AND VIRULENCE IN ERWINIA STEWARTII, AN IMPORTANT PATHOGEN OF CORN.

ON BEHALF OF OTHER PLANT PATHOLOGISTS, I STRONGLY URGE THIS COMMITTEE AND SECRETARY CALIFANO TO ACCEPT THE PROPOSED REVISED GUIDELINES AT THIS TIME SO THAT THERE WILL BE NO FURTHER DELAYS IN BEGINNING IMPORTANT RESEARCH ON GENETIC IMPROVEMENT OF CROPS, NITROGEN FIXATION, AND PLANT DISEASES AND OUR UNDERSTANDING OF THE ORGANISMS INVOLVED.

TICKER TAKES

from A.P. and U.P.I.

OFFICE OF INFORMATION ROOM 307 BUILDING 1 EXTENSION 65787

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B
NOBEL MEDICINE
STOCHKOLM, SWEDEN (AP) -- THE 1978 NOBEL PRIZE IN MEDICINE WAS AWARDED JOINTLY TODAY TO TWO AMERICANS AND A SWISS RESEARCHER FOR ENZYME GENETICAL RESEARCH. THE THREE ARE SWISS MICROBILOGY PROFESSOR WERNER ARBER OF BASEL AND DANIEL NATHANS AND HAMILTON O. SMITH, WHO BOTH WORK AT JOHNS HOPKINS UNIVERSITY IN BALTIMORE.

THE NOBEL COMMITTEE OF THE KAROLINSKA INSTITUTE OF MEDICINE CITED THEM FOR THE DISCOVERY OF RESTRICTION ENZYMES AND THEIR APPLICATION TO PROBLEMS OF MOLECULAR GENETICS.

RESTRICTION ENZYMES, DISCOVERED BY THE 49-YEAR-OLD ARBER, PROVIDE THE ''CHEMICAL KNIVES'' TO CUT GENES INTO DEFINED FRAGMENTS.

SMITH, 47, VERIFIED ARBER'S HYPOTHESIS AND NATHANS, 49, PIONEERED THE APPLICATION OF RESTRICTION ENZYMES TO GENETICS.

THEY WILL SHARE A PRIZE OF $165,000.
AP-WX-1012 09 03STT

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TELEGRAPHIC MESSAGE

NAME OF AGENCY	PRECEDENCE	SECURITY CLASSIFICATION
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE/OS/EXSEC	ACTION INFO:	
ACCOUNTING CLASSIFICATION 8-1990351 7580120	DATE PREPARED October 13, 1978	TYPE OF MESSAGE ☐ SINGLE ☐ BOOK ☐ MULTIPLE-ADDRESS
FOR INFORMATION CALL		
NAME Richard Cotton	PHONE NUMBER 245-7462	

THIS SPACE FOR USE OF COMMUNICATION UNIT

MESSAGE TO BE TRANSMITTED *(Use double spacing and all capital letters)*

TO:
DR. HAMILTON O. SMITH
JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE
725 N. WOLFE STREET
BALTIMORE, MARYLAND 20205

I LEARNED OF THE AWARD OF THE 1978 NOBEL PRIZE FOR MEDICINE TO YOU WITH A DEEP FEELING OF NATIONAL PRIDE AND WITH ADMIRATION FOR YOUR ACCOMPLISHMENTS.

YOUR KEY CONFIRMATION OF THE ORIGINAL DISCOVERY OF RESTRICTION ENZYMES -- AND YOUR SUBSEQUENT WORK WITH THESE ENZYMES -- HAS LED TO THEIR USE IN IMPORTANT RECOMBINANT DNA RESEARCH CARRIED OUT THROUGHOUT THE WORLD. RESTRICTION ENZYMES ARE NOW BEING USED IN HUNDREDS OF LABORATORIES TO STUDY THE STRUCTURE OF DNA -- WORK THAT MAY ULTIMATELY HELP US UNDERSTAND THE DIFFERENCE BETWEEN NORMAL CELLS AND CANCER CELLS. YOUR ASSOCIATION WITH THE RESEARCH PROGRAMS OF THIS DEPARTMENT OVER THE YEARS IS A SOURCE OF GREAT PRIDE TO US.

YOUR EFFORTS RICHLY DESERVE THE HIGH RECOGNITION YOU HAVE NOW RECEIVED, AND I OFFER MY MOST RESPECTFUL, PERSONAL CONGRATULATIONS.

JOSEPH A. CALIFANO, JR.
SECRETARY OF HEALTH,
EDUCATION, AND WELFARE

SECURITY CLASSIFICATION		
	PAGE NO.	NO. OF PGS.

STANDARD FORM 14
[illegible] 41 CFR, 101-35.306

14-102

TELEGRAPHIC MESSAGE

NAME OF AGENCY	PRECEDENCE	SECURITY CLASSIFICATION
DEPARTMENT OF HEALTH, EDUCATION, & WELFARE/OS/EXSEC	ACTION: INFO:	
ACCOUNTING CLASSIFICATION	**DATE PREPARED**	**TYPE OF MESSAGE**
8-1990351 7580120	October 13, 1978	☐ SINGLE ☐ BOOK ☐ MULTIPLE-ADDRESS
FOR INFORMATION CALL		
NAME	**PHONE NUMBER**	
RICHARD COTTON	245-7462	

THIS SPACE FOR USE OF COMMUNICATION UNIT

MESSAGE TO BE TRANSMITTED *(Use double spacing and all capital letters)*

TO:

DR. DANIEL NATHANS
JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE
725 N. WOLFE STREET
BALTIMORE, MARYLAND 21205

YOUR HONOR IN WINNING THE 1978 NOBEL PRIZE FOR MEDICINE BESTOWS TREMENDOUS CREDIT NOT ONLY ON YOU BUT ON THE QUALITY OF THE ENTIRE AMERICAN SCIENTIFIC COMMUNITY.

YOUR RESEARCH WITH RESTRICTION ENZYMES -- AND PARTICULARLY YOUR INNOVATIVE WORK IN MAPPING THE GENETIC STRUCTURE OF THE SV40 VIRUS USING RESTRICTION ENZYMES -- REPRESENTS A LANDMARK SCIENTIFIC ACHIEVEMENT WORTHY OF THE HONOR THAT THE KAROLINA INSTITUTE HAS BESTOWED UPON YOU. THE WIDESPREAD USE OF RESTRICTION ENZYMES IN RECOMBINANT DNA RESEARCH IS ELOQUENT TESTIMONY TO THE IMPORTANCE OF YOUR CONTRIBUTION. THE DEPARTMENT IS BOTH HONORED AND PLEASED TO HAVE PROVIDED SUPPORT FOR YOUR IMPORTANT WORK.

YOUR EFFORTS RICHLY DESERVE THE HIGH RECOGNITION YOU HAVE RECEIVED, AND I OFFER MY MOST RESPECTFUL, PERSONAL CONGRATULATIONS.

JOSEPH A. CALIFANO, JR.
SECRETARY OF HEALTH,
EDUCATION, AND WELFARE

SECURITY CLASSIFICATION		
	PAGE NO.	NO. OF PGS.

STANDARD FORM 14
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GSA FPMR (41 CFR) 101-35.306

14-102

TELEGRAPHIC MESSAGE

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ACCOUNTING CLASSIFICATION: 8-1990351 7580120	DATE PREPARED: October 13, 1978	TYPE OF MESSAGE: ☐ SINGLE ☐ BOOK ☐ MULTIPLE-ADDRESS
FOR INFORMATION CALL		
NAME: RICHARD COTTON	PHONE NUMBER: 245-7462	

THIS SPACE FOR USE OF COMMUNICATION UNIT

MESSAGE TO BE TRANSMITTED *(Use double spacing and all capital letters)*

TO:

PROFESSOR DOCTOR WERNER ARBER
C/O BIOZENTRUM VDER UNI
KLINGELBERGSTR.70
4056 BASEL SWITZERLAND

LET ME EXTEND WARM CONGRATULATIONS FOR THE RECOGNITION YOU HAVE RECEIVED BY WINNING THE 1978 NOBEL PRIZE IN MEDICINE. YOUR DISCOVERY OF RESTRICTION ENZYMES HAS MADE POSSIBLE EXTRAORDINARY RESEARCH INTO THE GENETIC BASIS OF CANCER, BIRTH DEFECTS, AND HUMAN DEVELOPMENT ITSELF.

YOUR EFFORTS RICHLY DESERVE THE HIGH RECOGNITION YOU HAVE RECEIVED, AND I OFFER MY MOST RESPECTFUL, PERSONAL CONGRATULATIONS.

JOSEPH A. CALIFANO, JR.
SECRETARY OF HEALTH,
EDUCATION, AND WELFARE

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GSA FPMR 41 CFR 101-35.306

14-102

95TH CONGRESS
2D SESSION

S. RES. 591

IN THE SENATE OF THE UNITED STATES

OCTOBER 13 (legislative day, OCTOBER 11), 1978

Mr. MATHIAS (for himself and Mr. SARBANES) submitted the following resolution; which was considered and agreed to

RESOLUTION

To congratulate Doctor Daniel Nathans and Doctor Hamilton O. Smith.

Whereas Doctor Daniel Nathans and Doctor Hamilton O. Smith of Johns Hopkins University were awarded the Nobel Prize in Medicine for research which led to the discovery and use of restriction enzymes and their application to genetics; and

Whereas their research demonstrated how these enzymes could be used to cut the DNA molecule for further study and thus analyze the structure of genes; and

Whereas this work will aid in the research toward understanding the gene function in cancer and various hereditary diseases; and

Whereas they are the first members of the active faculty of Johns Hopkins ever to receive the Nobel Prize for Medicine: Therefore, be it

Resolved, That the Senate congratulate both Doctor Nathans and Doctor Smith for this accomplishment and contribution to medicine and mankind and also congratulates Johns Hopkins University for sustaining the scientific and academic community within which this research could have occurred, and for maintaining the standard of excellence that has characterized the university since its founding.

95TH CONGRESS
2D SESSION

S. RES. 591

RESOLUTION

To congratulate Doctor Daniel Nathans and Doctor Hamilton O. Smith.

By Mr. MATHIAS and Mr. SARBANES

OCTOBER 13 (legislative day, OCTOBER 11), 1978

Considered and agreed to

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

October 26, 1978

NOTE TO: MEMBERS OF THE INTERAGENCY COMMITTEE
ON RECOMBINANT DNA RESEARCH

Enclosed are the complete minutes, as well as a summary, of the meeting of the Interagency Committee on Recombinant DNA Research that was held on October 12. Dr. Fredrickson has been reviewing your agency's comments and the proposed procedures for Interagency Committee participation under the NIH Guidelines with the DHEW Committee created by Secretary Califano to conduct the Department's September 15 hearing and advise the Secretary on the final Guidelines. The Committee will consider these procedural elements for inclusion in the Final Revised Guidelines within the next two weeks. It is the hope of Dr. Fredrickson and Mr. Peter Libassi, HEW Committee Chairman, that final Guidelines will be approved for release by the Secretary within the next three to four weeks.

Dr. Fredrickson has asked me to inform you that the NIH is sponsoring a three-day symposium for the Chairmen of approximately 153 Institutional Biosafety Committees. This meeting will be devoted to a review of the Guidelines, with special emphasis on their scientific aspects, their administrative implementation, and laboratory safety requirements. The meeting will be held November 19-21 at the Sheraton International Conference Center in Reston, Virginia. For further Information on this meeting, please contact Dr. William Gartland, Director of the Office of Recombinant DNA Activities, at NIH (496-6051).

I will keep you closely informed on developments concerning the Guidelines and procedural aspects involving the Interagency Committee.

Sincerely yours,

Joseph G. Perpich, M.D., J.D.
Associate Director for
Program Planning and Evaluation

2 Enclosures

INTERAGENCY COMMITTEE ON RECOMBINANT DNA RESEARCH

Summary Minutes of Meeting

October 12, 1978

National Institutes of Health

Bethesda, Maryland

The ninth meeting of the Interagency Committee took place on Thursday, October 12, from 2:30-4:30 at the National Institutes of Health. The meeting was chaired by Dr. Donald Fredrickson, Director of the NIH.

The meeting was devoted to a review of (1) the NIH Proposed Revised Guidelines, (2) the role of the Interagency Committee (IAC) in the revised Guidelines, and (3) agency comments on the Guidelines and the role of the IAC.

I. Review of the NIH Proposed Revised Guidelines (PRG)

Dr. Fredrickson opened the meeting by presenting an outline of events leading to the proposed revision of the NIH Guidelines, including:

- Phase I--the promulgation of the NIH Guidelines in June 1976.
- Phase II--the creation of the Interagency Committee in the Fall, 1976; subsequent oversight and legislative review in Congress, but no law; and the administration of the NIH Guidelines.
- Phase III--began with revised Guidelines proposed by the RAC in September 1977.

Before examining proposed procedural revisions of interest to the Committee, Dr. Fredrickson briefly summarized major technical changes in the Guidelines.

II. Proposed Role of the Interagency Committee (IAC) in the Proposed Revised Guidelines

A number of measures to encourage Federal agency participation in decisions on recombinant DNA research were outlined by Dr. Fredrickson.

A. RAC Membership

1. Recommendations for nomination of RAC members were requested in a Federal Register notice of July 1978.

2. All member agencies of the Interagency Committee will be invited to nominate a liaison member on the RAC. (Some agencies currently have these.)

B. Additional Procedures to Assure Consideration of Agency Views

1. Liaison membership would allow Federal agency participation in certain decisions.

2. In addition to liaison membership on the RAC, Federal agency participation will be specifically sought after certain RAC actions during the public comment period.

3. A three step appeal mechanism for RAC actions will be provided to Federal agencies.

C. Agency Resource

ORDA will provide consultation to all Federal agencies regarding the Guidelines.

D. Registration

In institutions where NIH funds recombinant DNA research two registration options are proposed.

E. Non-Compliance

If NIH receives an MUA or registration information for research funded by another Federal agency and ORDA believes it is in non-compliance, NIH will notify the Federal agency before notifying the institution where the research is conducted.

III. Agency Comments on the Proposed Revised Guidelines

The Committee was surveyed by Dr. Fredrickson for their comments on the Proposed Revised Guidelines. He noted those agency comments received in correspondence and requested that agencies in particular address the extent to which the above proposed procedural changes respond to their concerns.

A. Research Agencies

Department of Agriculture

Concern over prohibited agricultural pathogen risk assessment experiments and the release prohibition were cited. USDA will name a liaison member to the RAC. A Committee has been established within USDA to address recombinant DNA research. A registration scheme is in place with plans to share information with NIH. There are no special concerns with the experimental guidelines and it is generally felt that the proposed procedures will assist in USDA's particular concern over the release prohibition.

National Science Foundation

All containment procedures are endorsed by NSF. The National Science Board wants NSF to develop its own section on procedures; however it endorses the other three sections of the Guidelines. Dr. Lewis felt the procedures proposed address a majority of the concerns raised by Dr. Atkinson's letter. In addition, Dr. Lewis cited concern over the timeliness of NIH decisions following RAC action rather than with NIH's judgment. NSF agreed to share registration information with NIH including data on research conducted by small businesses funded by the agency.

Department of Defense

DoD reported that, scientifically, it is in agreement with the PRG and can accept the proposed procedural arrangements. In addition, DoD will send a formal letter noting its endorsement of the Guidelines.

Department of Energy

The Guidelines were endorsed by the DoE representative. Two issues of interest to DoE are (1) how to get advice on IBC composition and how to get these IBCs reviewed and (2) if NIH continues to do the primary registration for DoE funded projects, how to establish better communications with ORDA, in order to keep DoE informed.

National Aeronautics and Space Administration

Dr. Winter, representing NASA, reported satisfaction with the Proposed Revised Guidelines.

Veterans Administration

Although VA did not have a representative attending the meeting, Dr. Fredrickson outlined the main points raised in their letter and suggested the proposed role of the IAC in response to VA concerns.

B. Regulatory Agencies

Food and Drug Administration

Concern was expressed with large scale experiments, but it was felt that FDA liaison membership on the RAC would resolve this.

Environmental Protection Agency

Dr. Murray cited the main concerns with protection of the environment and voluntary controls that were contained in Mr. Costle's letter. No problems were reported by EPA on the proposed procedures.

Occupational Safety and Health Administration

The OSHA representative reported that some of the issues raised in Dr. Bingham's letter are addressed by the proposed procedures. Specific recommendations made by OSHA on the Proposed Revised Guidelines were mentioned; in particular, that grievance procedures are needed to cover those States not under OSHA.

Nuclear Regulatory Commission

No comments on or problems with the PRG were reported.

C. Other Agencies

Department of Interior

No comment was made on the Guidelines.

Department of Commerce

Concern over problems with proprietary data were registered. Input from private industry has been sought which indicates a willingness to follow the Guidelines but a concern over protection of proprietary information. Commerce reported an interest by private industry in NIH/ORDA advice.

Department of Transportation

It was reported that a letter from DoT has been sent raising concern over Guideline language regarding shipment. DoT reports that it currently cannot regulate shipment of recombinant DNA molecules.

Department of Justice

The Department of Justice representative reported no comment on the Guidelines.

U.S. Arms Control and Disarmament Agency

No comments on the Guidelines were cited.

Department of State

No comment was made on the Guidelines; however, the question was raised over the possibility of the need to review a previous Committee decision on the need for an international convention on recombinant DNA research or commerce. It was agreed that the need for such a convention was unnecessary in the light of WHO Guidelines on the shipment of hazardous agents, the commonality of containment guidelines in many countries, and the NIH policy providing for control of this research it funds abroad.

IV. Summary and Conclusion

The proposed procedural changes in the Guidelines were summarized by Dr. Fredrickson. He noted that these procedures had been developed largely in response to agency comments received on the Guidelines. With no objections noted, the Committee approved the proposed procedures subject to review by the DHEW Committee that was created by the Secretary to conduct the Department's September 15 hearing and advise the Secretary on the final Guidelines. Mr. Peter LiBassi, Office of General Counsel, serves as Chairman and Dr. Fredrickson serves as Vice-Chairman. It was agreed that there was a consensus among the Committee on the proposed procedures, and this message will be conveyed to the DHEW DNA Committee.

Dr. Fredrickson, in conclusion, emphasized the heightened responsibility the Interagency Committee will now have and the importance of future coordination and cooperation of agencies regarding recombinant DNA research.

Respectfully submitted,

Joseph G. Perpich, M.D., J.D.
Associate Director for
Program Planning and Evaluation

National Institutes of Health
Bethesda, Maryland

October 23, 1978

INTERAGENCY COMMITTEE ON RECOMBINANT DNA RESEARCH

Minutes of Meeting

October 12, 1978

National Institutes of Health

Bethesda, Maryland

The ninth meeting of the Interagency Committee took place on Thursday, October 12, from 2:30-4:30 at the National Institutes of Health. The meeting was chaired by Dr. Donald Fredrickson, Director of the NIH.

The meeting was devoted to a review of (1) the NIH Proposed Revised Guidelines, (2) the role of the Interagency Committee (IAC) in the revised Guidelines, and (3) agency comments on the Guidelines and the role of the IAC.

I. Review of the NIH Proposed Revised Guidelines (PRG)

Dr. Fredrickson opened the meeting by presenting an outline of events leading to the proposed revision of the NIH Guidelines, including:

- Phase I--the promulgation of the NIH Guidelines in June 1976.
- Phase II--the creation of the Interagency Committee in the Fall, 1976; subsequent oversight and legislative review in Congress, but no law; and the administration of the NIH Guidelines. It should be noted that this experience included the deferral of several Recombinant Advisory Committee (RAC) recommendations by the Director, NIH, due to the lack of discretion contained in the 1976 Guidelines. Because of this inflexibility, input from the Interagency Committee was primarily sought for Congressional policies rather than for review of RAC actions.
- Phase III--began with revised Guidelines proposed by the RAC in September 1977 and includes the Advisory Committee to the Director, NIH, public hearing in December 1977 at which Interagency Committee members participated; the NIH analysis and release of Proposed Revised Guidelines and accompanying Decision Document and Environmental Impact Assessment in July 1978; the DHEW public hearing September 15, 1978, again at which there was participation by Interagency Committee members; and the ongoing NIH analysis and DHEW review of letters from

public commentators and witness testimony. This current review process will include additional special meetings between the DHEW DNA Committee and representatives of industry and environmental/occupational groups.

Before examining proposed procedural revisions of interest to the Committee, Dr. Fredrickson briefly summarized major technical changes in the Guidelines.

- narrowed scope of definition,
- flexibility for containment,
- new nomenclature for host-vector systems in biological containment, and
- containment guidelines for experiments that represent a movement toward agreement with European Guidelines for this research.

II. Proposed Role of the Interagency Committee (IAC) in the Proposed Revised Guidelines

A number of measures to encourage Federal agency participation in decisions on recombinant DNA research were outlined by Dr. Fredrickson.

A. RAC Membership

1. Recommendations for nomination of RAC members were requested in a Federal Register notice of July 1978. These nominations will be solicited annually and agencies are encouraged to propose names. As a result of this open process, two plant and agricultural scientists suggested by USDA have been added recently to the RAC.

2. All member agencies of the Interagency Committee will be invited to nominate a liaison member on the RAC. (Some agencies currently have these.) This is to be a non-voting membership because the large number of Federal agencies would create too cumbersome a process for the operation of the RAC. Agency representatives, however, will be encouraged to participate in RAC discussion, stating their agency's concerns on scientific as well as other issues.

B. Additional Procedures to Assure Consideration of Agency Views

1. Liaison membership would allow Federal agency participation in certain decisions, for example, RAC interpretation of Guidelines and recommending changes in containment levels for experiments not considered in the Guidelines.

2. In addition to liaison membership on the RAC, Federal agency participation will be specifically sought after certain RAC actions during the public comment period, such as recommendations on waivers of prohibitions, new prohibitions, additions to the list of exemptions, certification of host-vector systems, and changes (including revisions and amendments) in the Guidelines. Plans call for all Interagency Committee members to receive advance Federal Register notices of these RAC actions for their comment.

   The possibility of a consensus meeting of the Interagency Committee on particular RAC actions, such as a recommendation to release a recombinant organism into the environment, is envisioned.

3. A three step appeal mechanism for RAC actions will be provided to Federal agencies:

   (1) consultation with ORDA

   (2) direct communication with the Director, NIH

   (3) provision for any agency to request a meeting of the Interagency Committee to consider RAC action in light of the agency's concern.

   It was noted by Dr. Fredrickson that there are currently no regularly scheduled Interagency Committee meetings; however, there will probably be a need for periodic meetings in the future.

C. Agency Resource

ORDA will provide consultation to all Federal agencies regarding the Guidelines.

D. Registration

In institutions where NIH funds recombinant DNA research two registration options are proposed:

- Federal agencies may elect to keep their own registries of projects they fund and then provide registration information to NIH. In this case, institutions would send Memoranda of Understanding and Agreement (MUAs) to the funding agency only and not to NIH.

- If an agency does not decide to keep a registry and provide NIH with registration information, then institutions will send MUAs to both NIH and the funding agency.

In institutions where recombinant DNA research is conducted and funded by Federal agencies other than NIH, it is hoped that the funding agency on a voluntary basis will provide registration information to NIH, in order to insure a more comprehensive national registry.

E. Non-Compliance

If NIH receives an MUA or registration information for research funded by another Federal agency and ORDA believes it is in non-compliance, NIH will notify the Federal agency before notifying the institution where the research is conducted. This process will be in effect if NIH-funded projects are being conducted at the institution. If there are no NIH funded projects, then only the Federal agency will be notified by NIH.

III. Agency Comments on the Proposed Revised Guidelines

The Committee was surveyed by Dr. Fredrickson for their comments on the Proposed Revised Guidelines. He noted those agency comments received in correspondence and requested that agencies in particular address the extent to which the above proposed procedural changes respond to their concerns.

A. Research Agencies

Department of Agriculture

Concern over prohibited agricultural pathogen risk assessment experiments and the release prohibition were cited. USDA will name a liaison member to the RAC. A Committee has been established within USDA to address recombinant DNA research and one of its functions will be to consider appeals from scientists funded by USDA. A registration scheme is in place with plans to share information with NIH. USDA endorses institutions having a single IBC, rather than a separate committee in its agricultural station. There are no special concerns with the experimental guidelines and it is generally felt that the proposed procedures will assist in USDA's particular concern over the release prohibition.

National Science Foundation

All containment procedures are endorsed by NSF. The National Science Board wants NSF to develop its own section on procedures; however it endorses the other three sections of the Guidelines. Dr. Lewis felt the procedures proposed address a majority of the concerns raised by Dr. Atkinson's letter. In addition, Dr. Lewis cited concern over the timeliness of NIH decisions following RAC action rather than with NIH's judgment. He would like an appeal mechanism for IBC actions by the PI to the RAC. Dr. Fredrickson noted the possibility of ORDA hearing PI complaints against IBCs and providing advice, but not necessarily overturning IBC decisions. It was agreed that it is important for IBCs to make the ultimate decision. NSF agreed to share registration information with NIH including data on research conducted by small businesses funded by the agency. It was noted that, so far, NSF has not encountered any problems in handling proprietary information.

Department of Defense

DoD reported that, scientifically, it is in agreement with the PRG and can accept the proposed procedural arrangements. In addition, DoD will send a formal letter noting its endorsement of the Guidelines.

Department of Energy

The Guidelines were endorsed by the DoE representative. It was noted that DoE has no special procedural needs such as those of NSF and agrees with the NIH position that in the case of an appeal by a PI, the final decision should rest with the IBC. Two issues of interest to DoE are (1) how to get advice on IBC composition and how to get these IBCs reviewed and (2) if NIH continues to do the primary registration for DoE funded projects, how to establish better communications with ORDA, in order to keep DoE informed. Dr. Fredrickson agreed that ORDA will need to work closely with agencies--especially in the development of a national registry.

National Aeronautics and Space Administration

Dr. Winter, representing NASA, reported satisfaction with the Proposed Revised Guidelines.

Veterans Administration

Although VA did not have a representative attending the meeting, Dr. Fredrickson outlined the main points raised in their letter and suggested the proposed role of the IAC in response to VA concerns.

B. Regulatory Agencies

Food and Drug Administration

Concern was expressed with large scale experiments, but it was felt that FDA liaison membership on the RAC would resolve this.

Environmental Protection Agency

Dr. Murray cited the main concerns with protection of the environment and voluntary controls that were contained in Mr. Costle's letter. The question was raised by USDA as to whether a double waiver for release of a recombinant organism was needed—one from the RAC and Interagency Committee and a separate one from EPA. The possibility of a requirement of an environmental impact statement for each decision for release was also raised. No problems were reported by EPA on the proposed procedures.

Occupational Safety and Health Administration

The OSHA representative reported that some of the issues raised in Dr. Bingham's letter are addressed by the proposed procedures. It was noted that OSHA receives calls requesting clarification on their authority regarding this research. If States do not have OSHA approved plans, then comparable State laws regarding employee protection obtain; that is, there are no States without any laws in this area.

Specific recommendations made by OSHA on the Proposed Revised Guidelines were mentioned; in particular, that grievance procedures are needed to cover those States not under OSHA. Dr. Fredrickson explained the NIH position on training and medical monitoring, two other issues raised by OSHA.

Nuclear Regulatory Commission

No comments on or problems with the PRG were reported.

C. Other Agencies

Department of Interior

No comment was made on the Guidelines.

Department of Commerce

Concern over problems with proprietary data were registered. Input from private industry has been sought which indicates a willingness to follow the Guidelines but a concern over protection of proprietary information. The Commerce representative noted that a

clause similar to FIFRA and FDA rules has been offered, that additional consideration of registration for private industry is needed, and that public members and conflict of interest restrictions on IBCs causes concern. In addition, Commerce reported an interest by private industry in NIH/ORDA advice.

Department of Transportation

It was reported that a letter from DoT has been sent raising concern over Guideline language regarding shipment. DoT reports that it currently cannot regulate shipment of recombinant DNA molecules.

Department of Justice

The Department of Justice representative reported no comment on the Guidelines.

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Dr. Fredrickson, in conclusion, emphasized the heightened responsibility the Interagency Committee will now have and the importance of future coordination and cooperation of agencies regarding recombinant DNA research.

Respectfully submitted,

Joseph G. Perpich, M.D., J.D.
Associate Director for
Program Planning and Evaluation

National Institutes of Health
Bethesda, Maryland

October 23, 1978

[4110-08-M]

RECOMBINANT DNA ADVISORY COMMITTEE

Meeting

Pursuant to Pub. L. 92-463, notice is hereby given of a meeting of the Recombinant DNA Advisory Committee at the National Institutes of Health, Building 1, Wilson Hall, 9000 Rockville Pike, Bethesda, Md. 20014, on October 30-31, 1978, from 9 a.m. to 5 p.m.

The entire meeting will be open to the public for consideration of:

Report of Working Group on Lower Eukaryotic Host-Vector Systems.
Report of Working Group on Prokaryote Host-Vectors Other Than *E. coli* K-12.
Organisms that exchange genetic information.
Review of protocols for required containment levels.
Requests for lowering of containment levels on the basis of characterization of clones.
Other matters requiring necessary action by the Committee.

Attendance by the public will be limited to space available. Dr. William J. Gartland, Executive Secretary, Recombinant DNA Advisory Committee, National Institutes of Health, Building 31, room 4A52, telephone 301-496-6051, will provide materials to be discussed at the meeting, rosters of committee members, and substantive program information. A summary of the meeting will be available at a later date.

Dated: October 3, 1978.

SUZANNE L. FREMEAU,
Committee Management Officer, NIH.

[FR Doc. 78-28766 Filed 10-12-78; 8:45 am]

[4110-08-M]

RECOMBINANT DNA ADVISORY COMMITTEE

Renewal

The Director, National Institutes of Health, announces the renewal on June 30, 1978, of the Recombinant DNA Advisory Committee, under the Authority of section 222 of the Public Health Service Act (42 U.S. Code 217a). Such advisory committees shall be governed by the provisions of the Federal Advisory Committee Act, as amended (Pub. L. 92-463) setting forth standards governing the establishment and use of advisory committees.

Authority for the above committee will expire on June 30, 1980, unless the Secretary formally determines that continuance is in the public interest.

Dated: October 11, 1978.

DONALD S. FREDRICKSON,
Director,
National Institutes of Health.

[FR Doc. 78-30062 Filed 10-24-78; 8:45 am]

AGENDA

WORKSHOP FOR CHAIRMEN OF INSTITUTIONAL BIOSAFETY COMMITTEES

Sheraton International Conference Center
Reston, Virginia

November 19-21, 1978

Sponsored by

The National Cancer Institute

The National Institute of Allergy and Infectious Diseases

The National Institute of General Medical Sciences

Sunday, November 19

4:00 - 6:00 p.m.	Registration, Lobby
6:00 - 7:00 p.m.	Reception, Room 9-10
7:00 - 8:30 p.m.	Banquet, Room 9-10 *Dr. William Gartland, Jr.*, Presiding Banquet Address: Risk Assessment Experiments *Dr. Malcolm Martin*

Monday, November 20

7:00 - 8:30 a.m.	BREAKFAST BUFFET, Derby Room, Second Level
7:30 - 8:30	Late Registration, Lobby

PLENARY SESSION I — PRESENTATION OF NIH GUIDELINES, Room A, B
Session Moderator: Dr. William Gartland, Jr.

8:30	INTRODUCTION *Dr. William Gartland, Jr.*
8:45	Scope of the Guidelines *Dr. Bernard Talbot*
9:15	Physical Containment *Dr. Emmett Barkley*
9:45	Biological Containment *Dr. Susan Gottesman*
10:15 - 10:45	COFFEE BREAK, Lobby
10:45	Classification of Experiments Using the E. Coli K-12 and Other Prokaryotic Host-Vector Systems *Dr. Susan Gottesman*

Monday, November 20 (Continued)

11:15 a.m.	Classification of Experiments with Eukaryotic Host-Vectors *Dr. Malcolm Martin*
11:45	Roles and Responsibilities *Dr. Joseph G. Perpich*
12:15 - 1:30 p.m.	LUNCH BUFFET, Derby Room, Second Level
1:30 - 2:15	NIH Policies and Administrative Procedures for Experiments Subject to the NIH Guidelines *Dr. William Gartland, Jr.*

PLENARY SESSION II — OPERATIONS OF THE INSTITUTIONAL BIOSAFETY COMMITTEE (IBC)
Session Moderator: Dr. Emmett Barkley

2:15 - 3:30 Panel Discussion, Room A, B

Recordkeeping, minutes, and reporting
Dr. Edward Adelberg

Certification of practices, equipment and facilities, the development of emergency plans, and the Biological Safety Officer
Dr. Emmett Barkley

Organization and membership and relationship with institutional management
Dr. Rose Litman

Public participation and community relations
Dr. Donald Peterson

Monitoring of compliance, and assessment of containment levels
Dr. Robert Simoni

3:30 - 4:00 COFFEE BREAK, Lobby

4:00 - 5:00 WORKSHOP SESSION I

Concurrent Workshops to Discuss the Operations of the IBC - *each group chaired by one panel member*

Room	Chairman	Participants divide alphabetically
1	*Dr. Edward Adelberg*	A - B
2	*Dr. Emmett Barkley*	C - G
3	*Dr. Rose Litman*	H - L
4	*Dr. Donald Peterson*	M - R
A	*Dr. Robert Simoni*	S - Z

Monday, November 20 (Continued)

6:00 p.m. SOCIAL HOUR, Room 9, 10

7:00 DINNER, Room 9, 10

Dr. William Gartland, Jr., Presiding
Evening Address
Mr. Peter Libassi

Tuesday, November 21

7:00 - 8:30 a.m. BREAKFAST BUFFET, Derby Room, Second Level

8:30 WORKSHOP SESSION II
Participants will attend all three sessions, scheduled alphabetically

Room 1. Administrative Procedures, MUA Review, and the Assessment of Containment Levels
Dr. Barban, Dr. Resnick, and Dr. Gartland

Room 2. Training and Certification of Physical Containment Safeguards
Dr. Barkley, Dr. Nutter, Mr. Oviatt, Dr. Ginsberg

Room 3. Medical Surveillance and Emergency Procedures
Dr. Richardson, Dr. Wasserman

8:30 - 10:00

Room	Group
1	A - G
2	H - P
3	Q - Z

10:00 - 10:30 COFFEE BREAK, Lobby

10:30 - 12:00

Room	Group
1	H - P
2	Q - Z
3	A - G

12:00 - 1:00 p.m. LUNCH BUFFET, Derby Room

1:00 - 2:30

Room	Group
1	Q - Z
2	A - G
3	H - P

2:00 COFFEE AVAILABLE IN LOBBY UNTIL 3:30

Tuesday, November 21 (Continued)

PLENARY SESSION III

2:30 p.m. — Conclusions
Dr. William Gartland, Jr., Session Moderator

Concluding Address
Dr. Donald Fredrickson

3:00 — Adjournment

SAFETY DISPLAY

During the two-day workshop there will be a safety display and a staff of biological safety officers available to consult with IBC chairmen on matters pertaining to physical containment and the certification of facilities and containment equipment.

DISPLAY HOURS

Monday	10:15 a.m.	—	6:00 p.m.
Tuesday	8:30 a.m.	—	1:00 p.m.

HEW NEWS

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

FOR RELEASE IN A.M. PAPERS
Friday, December 29, 1978

John Blamphin--(202) 245-6343

Fourteen new members have been appointed to the Department of Health, Education, and Welfare's Recombinant DNA Advisory Committee, HEW Secretary Joseph A. Califano, Jr., announced today. The new appointments enlarge the committee from 11 to 25 members, and significantly enhance its capacity to deal with the legal, ethical and other non-scientific issues which surround recombinant DNA research.

The Advisory Committee serves as the principal advisory body to the HEW Secretary and to the Director of the National Institutes of Health on recombinant DNA policy.

"While this committee must possess great scientific competence, it is important that it also be equipped to offer the best possible advice on the ethical, legal, public health and environmental issues which relate to recombinant DNA research," the Secretary said. "I believe that the members of this committee will offer us excellent technical and broader policy guidance on these issues as we move forward in this new field of biological exploration."

The panel will give advice on new types of bacteria for use in recombinant DNA experiments, on whether certain presently prohibited experiments should be conducted, whether additional categories of research should be exempted from the guidelines, and on future changes in the guidelines.

(More)

Revised guidelines covering the conduct of recombinant DNA research were announced by the Secretary December 17. The new guidelines increase public participation significantly at both the local and national level in the advisory and biosafety committees the program requires.

Recombinant DNA molecules contain segments of DNA which have been combined in the test tube. The research techniques used to produce recombined molecules of deoxyribonucleic acid (DNA), the complex chemical that codes genetic information for all living cells, hold promise for advancing the understanding of fundamental biological processes. Moreover, this research may also have potential for the commercial production of needed biological materials and agricultural products.

A complete list of members of the Recombinant DNA Advisory Committee is attached.

Additional callbacks

Dr. Bernard Talbot
(301) 496-3561

Dr. William Gartland
(301) 496-6051

# # #

NIH Recombinant DNA Advisory Committee

Current Members

1. Allan Campbell, Ph.D., Professor, Department of Biology, Stanford University, Stanford, California

2. Peter Day, Ph.D., Chief, Division of Genetics, Connecticut Agricultural Experiment Section, New Haven, Connecticut

3. Susan Gottesman, Ph.D., Senior Investigator, Laboratory of Molecular Biology, National Cancer Institute, Bethesda, Maryland

4. Richard Hornick, M.D., Director, Division of Infectious Diseases, School of Medicine, University of Maryland, Baltimore, Maryland

5. Elizabeth Kutter, Ph.D., Member of the Faculty in Biophysics, The Evergreen State College, Olympia, Washington

6. Emmette Redford, Ph.D., LL.D., Ashbel Smith Professor of Government and Public Affairs, Lyndon B. Johnson School of Public Affairs, University of Texas at Austin, Austin, Texas

7. Wallace Rowe, M.D., Chief, Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland

8. Jane Setlow, Ph.D., DNA Chairperson, Biologist, Brookhaven National Laboratory, Upton, New York

9. John Spizizen, Ph.D., Chairman, Department of Microbiology, Scripps Clinic & Research Foundation, La Jolla, California

10. LeRoy Walters, Ph.D., Director, Center for Bioethics, Kennedy Institute, Georgetown University, Washington, D.C.

11. Milton Zaitlin, Ph.D., Professor, Department of Plant Pathology, Cornell University, Ithaca, New York

New Members

1. A. Karim Ahmed, Ph.D., Senior Staff Scientist, Natural Resources Defense Council, New York, New York

2. David Baltimore, Ph.D., Nobel Laureate, American Cancer Society Professor of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts

3. Francis Broadbent, Ph.D., Professor of Soil Microbiology Department of Land, Air, and Water Resources, University of California, Davis, Davis, California

4. Zelma Cason, Chief of Cytotechnology, Department of Cytology, University of Mississippi Medical Center, Jackson, Mississippi

5. Richard Goldstein, Ph.D., Assistant Professor of Microbiology & Molecular Genetics, Harvard Medical School, Boston, Massachusetts

6. Patricia King, Professor of Law, Georgetown University Law Center, Washington, D.C.

7. Sheldon Krimsky, Ph.D., Acting Director, Program in Urban Social & Environmental Policy, Tufts University, Medford, Massachusetts

8. Richard Novick, M.D., Chairman of Plasmid Biology, Public Health Research Institute, New York, New York

9. David Parkinson, B.M., B.Ch., Associate Professor of Occupational Health, University of Pittsburgh, Pittsburgh, Pennsylvania

10. Ramon Pinon, Ph.D., Assistant Professor of Biology, University of California, San Diego, San Diego, California

11. Samuel Proctor, Ph.D., Professor of Education, Graduate School of Education, Rutgers University, New Brunswick, New Jersey

12. Ray Thornton, retiring member, U.S. House of Representatives (D. Ark.) and Chairman of Subcommittee on Science, Research and Technology

13. Luther Williams, Ph.D., Associate Professor of Biology and Assistant Provost, Department of Biological Sciences, Purdue University, West Lafayette, Indiana

14. Frank Young, M.D., Ph.D., Professor and Chairman, Department of Microbiology, University of Rochester, Rochester, New York

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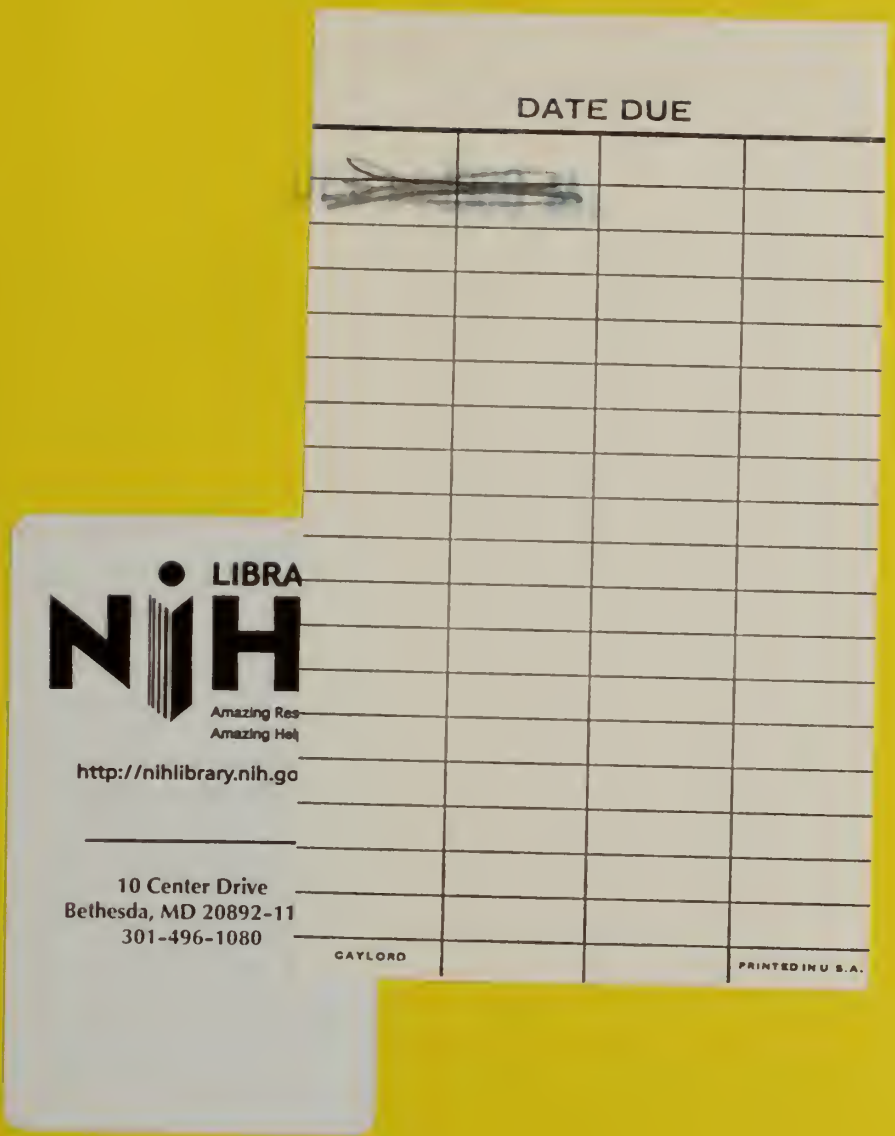

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